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Total syntheses of trikentrins and of herbindoles

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Dedicated with deep respect to Professor J.M. Riveros on the occasion of his 70th birthday

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Contents

1. Introduction

Since ancient times, natural compounds have been investigated, aiming mainly a solution to heal or to relief the symptoms of diseases. Plants and terrestrial organisms were the first to be intensively studied. However, in the last decades, the chemistry of marine natural products become of great interest due to the enormous molecular diversity that can be found on such environment, including structures that are not usually found on terrestrial living organisms, such as halogenated compounds.[1–4] This diversity occurs due to drastic conditions of marine environment such as high pressure, temperature, and salts concentration.[1] The statement of Faulkner[5] for one of the specialties in this field clearly describes the importance of marine natural products in science: '*Studies of marine toxins will continue to be of importance well into the next century and probably for as long as human consumption of*

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seafood continues'.[6] Among the marine organisms, sponges (porifers) and ascidians (tunicates) are the most widely investigated.[1] The main reasons are: (i) easy gathering (shallow water, although deep-water species can also be found); and (ii) use of chemical defense since they are sessile organisms. In this scenario, Capon and his group isolated in 1986 from the marine sponge *Trikentrion flabelliforme* collected in Australian coast, five new indole alkaloids: (+)-*trans*-trikentrin A, (+)-*cis*-trikentrin A, (−)-*trans*-trikentrin B, *cis*-trikentrin B and *iso*-*trans*-trikentrin B (Fig. 1). The last two were isolated as a 3:2 mixture. Although pure enantiomers were isolated, the absolute configurations were assigned only after total synthesis. All five compounds showed antimicrobial activity, determined in a standard disc assay, against cultures of the gram positive bacteria *Bacillus subtillis*, by measuring zones of inhibition.[7]

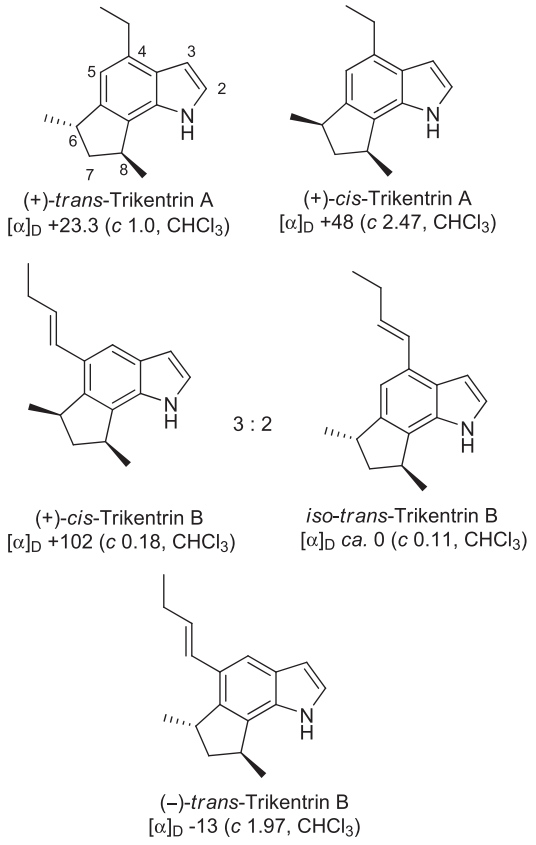


Figure 1. Structure of trikentrins.

From *Axinella* sp., an orange sponge species collected in the Australian coast, three other indoles structurally similar to the trikentrins were isolated by Scheuer and his group.[8] These compounds were denominated herbindole A, herbindole B, and herbindole C. The cytotoxic activity against KB cells (nasopharyngeal carcinoma) as well as appetite inhibiting activity in fishes was observed for all the herbindoles. The IC_{50} value for herbindole A is 5 μg/mL, >10 μg/mL for herbindole B, and 10 μg/mL for herbindole C. The feeding deterrence was measured by coating a mixture of all three herbindoles on thin strips of squid fastened to a reef and comparing the eaten amount with a control group of untreated squid. The results (p=0.005) showed that 48.1±10% for treated squid and 80.6±6.4% of the control squid were eaten. Although pure enantiomers were isolated, only the cis relative configuration between methyl groups was assigned. Additionally, $[\alpha]_D$ values were not measured. The absolute configuration of herbindole A was assigned later during total synthesis. Based on that the absolute configuration of herbindoles B and C was suggested.

A structural feature of trikentrins and of herbindoles is the absence of a substituent in the C3 position. This is not typical because most of the natural indole alkaloids have the tryptophan amino acid as a precursor in biosynthesis (e.g., ergot, aspidosperm, strychno, and carbazole alkaloids),[9] and thus possesses a side chain at C3. Furthermore, trikentrins and herbindoles are polyalkylated indoles that bear a 1,3-dimethylcyclopentanic moiety fused to the indole ring and one or two alkyl (or alkenyl) substituents on the benzene ring (see Figs. 1 and 2). The unusual structure of these alkaloids and the possibility to find other biological properties have stimulated several research groups to synthesize them. In this context, this review discusses the syntheses carried out up to this date for all trikentrins and all herbindoles.

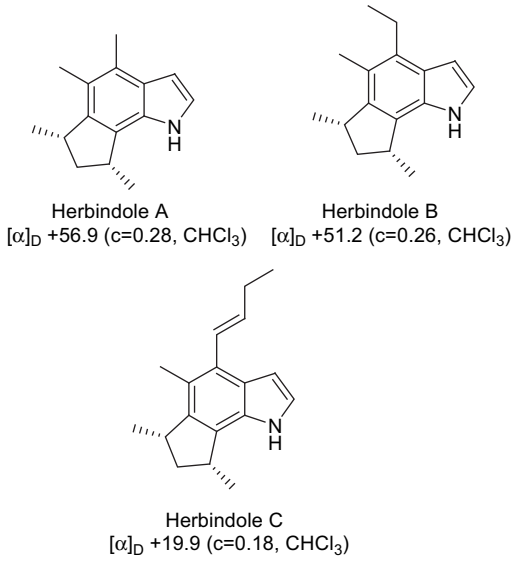


Figure 2. Structure of herbindoles.

2. Total synthesis of trikentrins and herbindoles

A summary of the total syntheses of trikentrins and herbindoles is presented in Table 1. Since the late 80s the total synthesis of trikentrins and herbindoles has been continuously reported, although a gap in the late 90s and early 2000s can be observed. More syntheses of the alkaloids that bear a cis relationship between the methyl groups were reported than the corresponding trans. For the discussion in this review, the total syntheses of trikentrins and herbindoles were grouped according to the research group and, consequently, by the synthetic strategy: MacLeod (radical cyclization), Natsume (indolization of pyrroles), Kanematsu (intramolecular Diels–Alder of allenic dienamides), Boger (heteroaromatic Diels–Alder), Blechert (Heck coupling), Kerr (Diels–Alder of iminoquinones), Funk (electrocyclic ring closing), Buszek (cycloaddition reaction), and Silva (ring contraction reaction).

2.1. Syntheses of MacLeod and co-workers

Intramolecular radical cyclizations are highly regioselective for the formation of five-membered ring derivatives,[27] because the 5-*exo* cyclization mode is kinetically favored due to the lower energy of the transition state, when compared to that of the corresponding 6-*endo* product.[28–30] This transformation has been applied in the total synthesis of several natural products,[31] including the racemic total synthesis of *cis*- and *trans*-trikentrin A.[10,11] MacLeod and his group envisioned that trikentrins A could be obtained by thermolysis of unsaturated azides (**1** and **4**). These intermediates would

Table 1
Summary of the syntheses of trikentrins and herbindoles

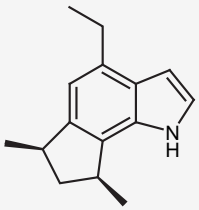
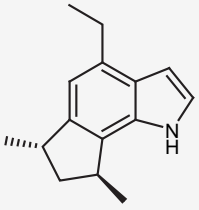
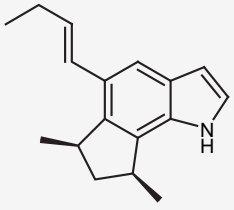
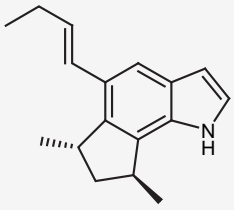
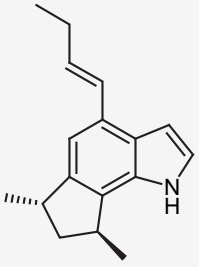
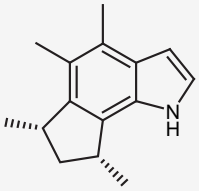
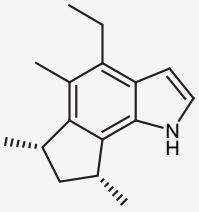
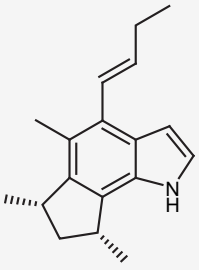
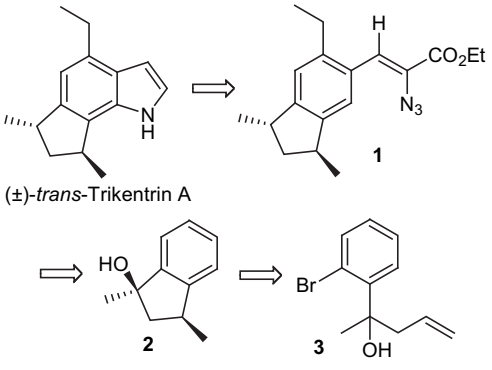
Molecule	Syntheses[a]
 *cis*-Trikentrin A	1988; MacLeod;[10,11] racemic; 12 steps 1989; Natsume;[12] asymmetric (not natural); 9 steps 1990; Natsume;[13] racemic; 6 steps 1991; Boger;[14] racemic; 7 steps 1994; Natsume;[15] asymmetric (natural); 17 steps 1995; Blechert;[16] racemic; 8 steps 2006; Funk;[17] racemic; 11 steps 2007; Kerr;[18] racemic; 19 steps 2009; Buszek;[19] racemic; 9 steps
 *trans*-Trikentrin A	1989; Natsume;[12,13] asymmetric (not natural); 9 steps 1990; MacLeod;[11] racemic; 11 steps 1990; Natsume;[13] racemic; 6 steps 1991; Boger;[14] racemic; 8 steps 2008; Silva;[20] racemic; 20 steps
 *cis*-Trikentrin B	1989; Kanematsu;[21] racemic; 18 steps. 1990; Natsume;[13] racemic; 7 steps 1993; Natsume;[15,22] asymmetric (natural); 16 steps 1996; Kanematsu;[23] asymmetric (natural); 30 steps 2005; Kerr;[24] racemic; 15 steps 2006; Funk;[17] racemic; 13 steps
 *trans*-Trikentrin B	1990; Natsume;[13] racemic; 7 steps 1993; Natsume;[15,22] asymmetric (not natural); 16 steps
 *iso-trans*-Trikentrin B	1998; MacLeod;[25] racemic; 15 steps 1990; Natsume;[13] racemic; 6 steps 1993; Natsume;[15,22] asymmetric (not natural); 18 steps
 Herbindole A	1992; Natsume;[15,26] asymmetric (not natural); 16 steps 2007; Kerr;[18] racemic; 18 steps 2009; Buszek;[19] racemic; 9 steps

Table 1 (*continued*)

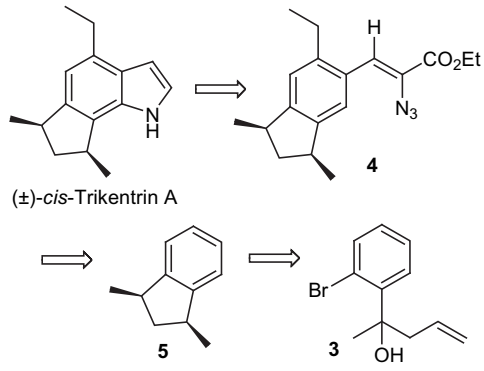
Molecule	Syntheses[a]
 Herbindole B	1992; Natsume;[15,26] asymmetric (not natural); 17 steps 2005; Kerr;[24] racemic; 19 steps 2007; Kerr;[18] racemic; 19 steps
 Herbindole C	1992; Natsume;[15,26] asymmetric (not natural); 18 steps

[a] Number of steps of the longest linear sequence from a commercially available compound.

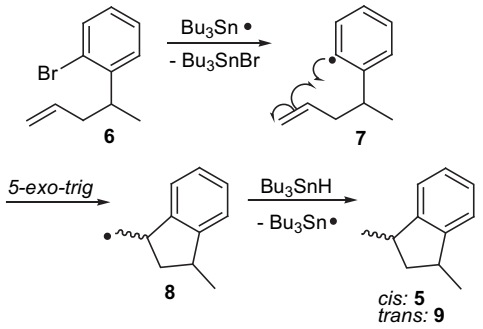
be obtained from an appropriate indane (**2** or **5**, respectively), which could be prepared through a radical cyclization from the same compound **3** (Schemes 1 and 2). This reaction, catalyzed by AIBN, should be performed on a suitable arylbromine with a terminal alkene side chain. After the tributyltin radical formation, the arylbromine **6** would be transformed into the aryl radical **7**. This intermediate would undergo a 5-*exo*-*trig* cyclization generating the alkyl radical **8**. Reaction with tin hydride would lead to the desired 1,3-dimethylindane (Scheme 3).



Scheme 1.



Scheme 2.



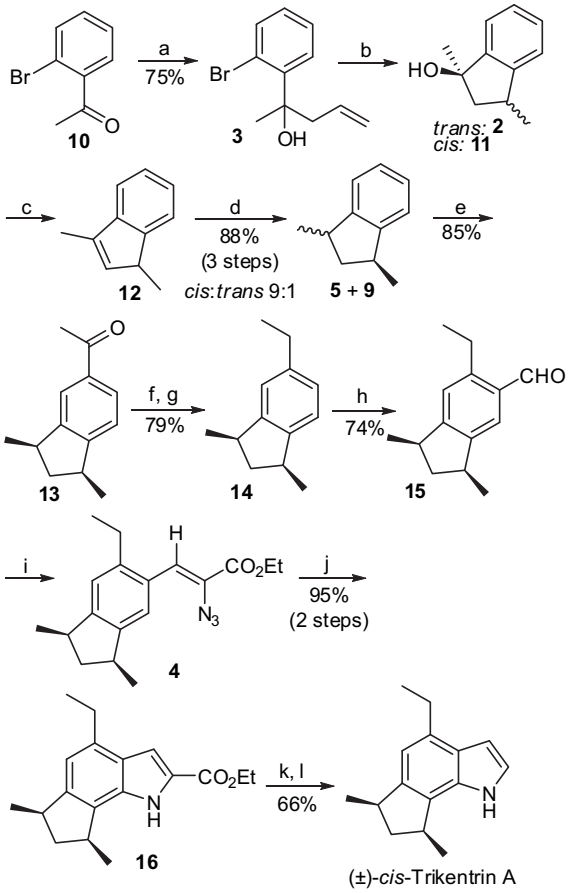
Scheme 3.

In 1988, a 12-step synthesis of (±)-*cis*-trikentrin A was concluded starting from the nucleophilic addition of allyl magnesium bromide to 2-bromoacetophenone (**10**) generating the alcohol **3**.[10] This compound has adequate functional groups to undergo an intramolecular radical cyclization mediated by AIBN. This reaction led to a cis/trans mixture of indanols **2** and **11** (ratio not informed). Dehydration of these alcohols and hydrogenation of indene **12**, generated the 1,3-dimethylindanes **5** and **9**, as a 9:1 mixture, respectively. The regioselective acylation of **13** followed by two reduction reactions led to the ethyl indane **14**, which was formylated with Cl_2HCOMe and $TiCl_4$, giving **15**. Subsequently, **15** was transformed into the unsaturated azide **4** by a Knoevenagel-like reaction. The indole **16** was obtained through the thermolysis of **4** and the minor trans isomer was removed by chromatography column at this point. The mechanism of the Hemetsberger synthesis that leads to indole **16** is not established.[32] However, azirinic-like intermediates such as **17** were isolated[33] (Scheme 5). The ester group of **16** was hydrolyzed to the corresponding carboxylic acid, which was decarboxylated through a vacuum pyrolysis, giving the target molecule. Despite the drastic conditions, this step was achieved in 89% yield (Scheme 4).

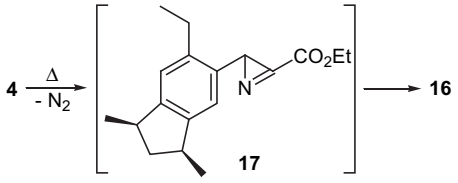
In 1990, the synthesis of (±)-*trans*-trikentrin A[11] was completed by a sequence analogous to that followed for the synthesis of *cis*-trikentrin A, excepting the formation of the indanic moiety. In the synthesis of (±)-*trans*-trikentrin A, a radical cyclization of alcohol **3** resulted in a 1:1 mixture of the indanols **11** and **2**, which were separated by column chromatography. The isomer **2** led to the isomeric indanes **9** and **5** in a 9:1 ratio, through a hydrogenolysis reaction with Raney nickel. This intermediate led to (±)-*trans*-trikentrin A following the methodology developed in the synthesis of *cis*-trikentrin A (Scheme 4). Yields of steps c–j were not reported (Scheme 6).

Some years later, in 1998, MacLeod and co-workers concluded the total synthesis of (±)-*iso*-*trans*-trikentrin B in 15 steps.[25] In this synthesis, the target molecule was obtained from an unsaturated azide (**22**), similar to the total synthesis of trikentrins A of the same group (Schemes 1 and 2).[34] Moreover, the azide was also obtained from an indane (**2**). However, the required *trans*-indane **2** was prepared from the 1-indanone **23** (Scheme 7) avoiding the radical cyclization, because this reaction showed low diastereoselectivity in previous works.

The synthesis starts with a Friedel–Crafts reaction with benzene and crotonic acid followed by an electrophilic conjugated addition leading to indanone **23**. The reaction of this intermediate with methyl magnesium iodide led to alcohol **2** in good selectivity. The subsequent hydrogenolysis reaction was carried out as for the synthesis of (±)-*trans*-trikentrin A shown in Scheme 6, also leading to indanes **9** and **5** in a 9:1 ratio, respectively. The need for a different substituent in C4 position of the indole skeleton changed the reaction sequence followed in previous syntheses. A Friedel–Crafts acylation with butyryl chloride followed by reduction of the ketone moiety, furnished the alcohol **24**. This intermediate was brominated



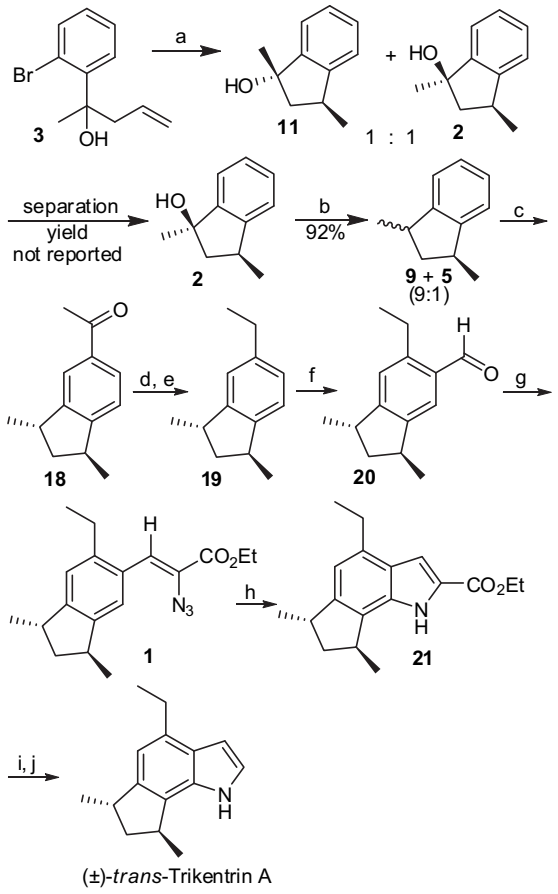
Scheme 4. Reagents and conditions: (a) allyl magnesium bromide, Et_2O; (b) Bu_3SnH, AIBN, C_6H_6; (c) H^+, $CHCl_3$; (d) H_2, Pd/C, $CHCl_3$; (e) AcCl, $AlCl_3$, CH_2Cl_2; (f) $NaBH_4$, MeOH; (g) H_2, Pd/C, $CHCl_3$; (h) Cl_2HCOCH_3, $TiCl_4$, CH_2Cl_2; (i) $N_3CH_2CO_2Et$, NaOMe, EtOH; (j) Δ; (k) KOH, dioxane/H_2O; (l) 800 °C, 0.003 mmHg.



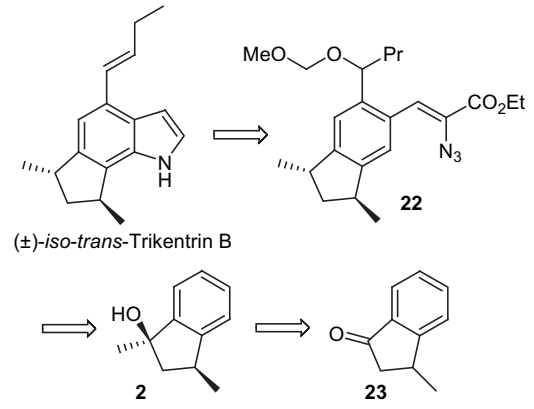
Scheme 5.

and formylated generating aldehyde **26**, which led to **22** after treatment with the β-azido ester under basic conditions. The indole **27** was obtained as in precedent syntheses, but a rhodium catalyst was used in the decarbonylation reaction allowing reaction conditions to be milder than before (compare to Scheme 4). The benzylic ether was eliminated with dimethylboron bromide and triethylamine, leading to (±)-*iso*-*trans*-trikentrin B (Scheme 8).

The authors suggested that the benzylic ether elimination was triggered by removal of the proton of the indolic nitrogen by triethylamine. The first step would be the transformation of the ether group of **29** into a better leaving group by reacting it with dimethylboron bromide (**30**). The complex **31** thus formed would generate the intermediate **32** in the presence of NEt_3. Allylic deprotonation and re-aromatization of **32** would lead to (±)-*iso*-*trans*-trinkentrin B (Scheme 9). In conclusion, MacLeod and co-workers were the first to perform the synthesis of trikentrin alkaloids. During their work racemic synthesis of *cis*-trikentrin A, *trans*-trikentrin A, and iso-*trans*-trikentrin B was accomplished. The thermolysis of unsaturated azides was used in all synthesis to construct the indole ring.



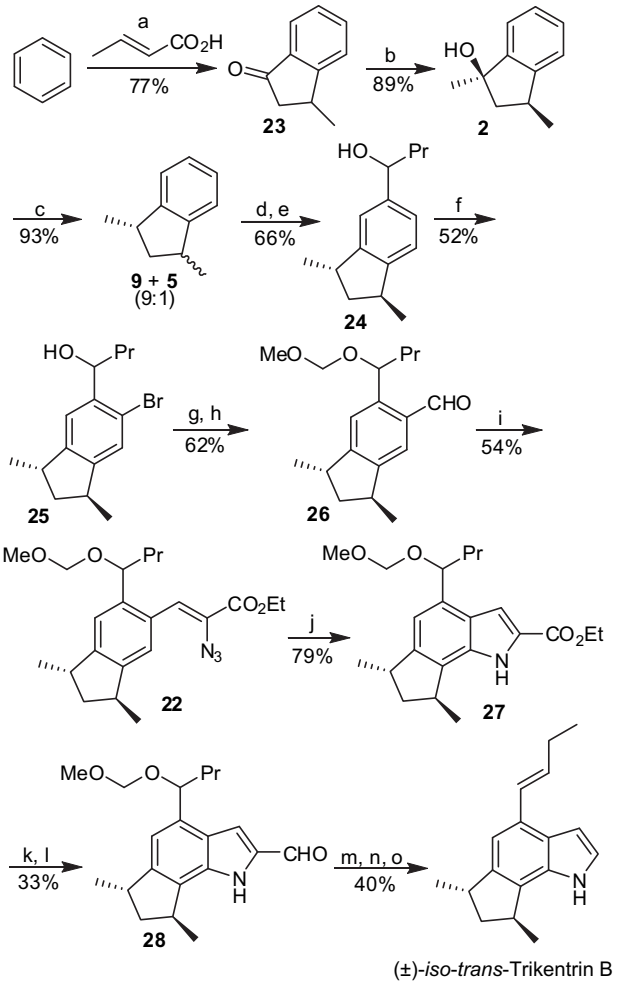
Scheme 6. Reagents and conditions: (a) Bu_3SnH, AIBN, C_6H_6; (b) Raney nickel W7; (c) AcCl, $AlCl_3$, CH_2Cl_2; (d) $NaBH_4$, MeOH; (e) H_2, Pd/C, $CHCl_3$; (f) Cl_2HCOCH_3, $TiCl_4$, CH_2Cl_2; (g) $N_3CH_2CO_2Et$, NaOMe, EtOH; (h) Δ; (i) KOH, dioxane/H_2O; (j) 800 °C, 0.003 mmHg.



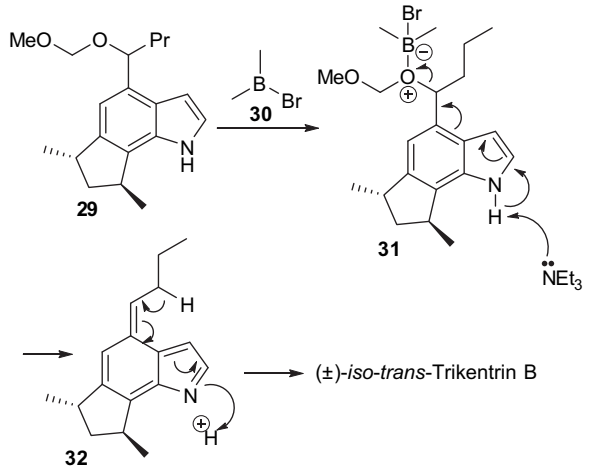
Scheme 7.

2.2. Syntheses of Natsume and co-workers

The main contribution of the syntheses of Natsume and co-workers was the assignment of the absolute configuration of trikentrins. In their route, trikentrins and herbindoles could be synthesized by a pyrrole indolization reaction with appropriate substituents, according to the structure of the natural product. A representative example of this reaction is shown in Scheme 10. Treating pyrrole derivatives such as **33** with protic acid leads to hydrolysis of hydrazone, giving **34**. Intramolecular attack of pyrrole to the protonated carbonyl in **34** generates the intermediate **35**, which undergoes aromatization through dehydration, forming the indole **36**.

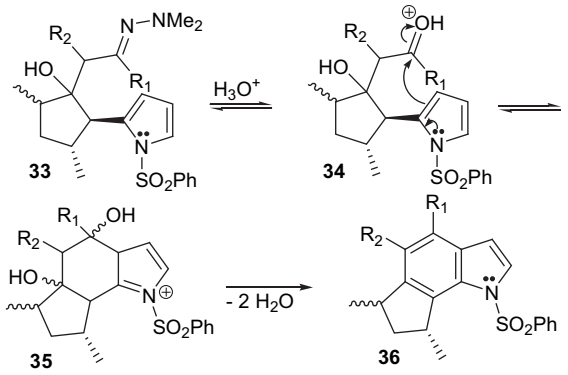


Scheme 8. Reagents and conditions: (a) $AlCl_3$, reflux, 17 h; (b) (i) MeMgI, Et_2O; (ii) HCl, H_2O; (c) Raney nickel W7, EtOH, reflux, 2 h; (d) butyryl chloride, $AlCl_3$; (e) $NaBH_4$, MeOH; (f) *t*-BuLi, CBr_4, heptane; (g) $MeOCH_2Cl$, DMAP, CH_2Cl_2, *i*-Pr_2EtN, rt, 17 h; (h) heptane, *n*-BuLi, DMF; (i) $N_3CH_2CO_2Et$, Na, EtOH; (j) toluene, 135 °C, 2 h; (k) DIBAL-H, toluene; (l) MnO_2; (m) bis(triphenylphosphine)(carbonyl)rhodium(I), 1,3-bis(diphenylphosphino)propane; (n) Me_2BBr, CH_2Cl_2, rt; (o) Et_3N, rt.



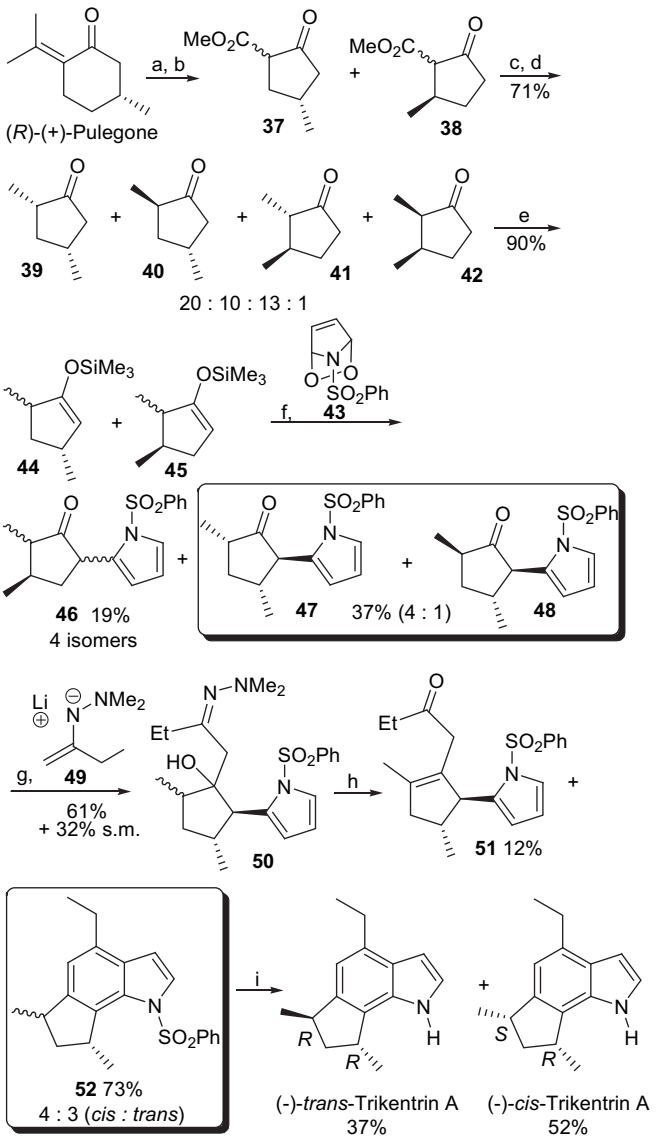
Scheme 9.

Considering that enantiomerically enriched pyrrole derivatives, such as **33**, can be obtained, this strategy was employed in the asymmetric synthesis of a mixture of (−)-*cis*-trikentrin A and (−)-*trans*-trikentrin A, which are the antipodes of the natural products.[12] The starting material of the synthesis was the



Scheme 10.

monoterpene (*R*)-(+)-pulegone, which led to (*R*)-3-methyladipic acid under oxidative cleavage conditions with $KMnO_4$. This acid was converted into an inseparable mixture of cyclopentanones **37** and **38**, through esterification and Dieckmann condensation. An α-methylation followed by decarboxylation afforded an inseparable mixture of isomeric dimethylcyclopentanones **39**, **40**, **41**, and **42**. Then, the corresponding silyl enol ethers **44** and **45** were prepared and condensed with **43**, giving a 4:1 mixture of **47** and **48** (37% yield), as well as four isomers of **46** (19% yield). The isomers **47**/**48** were treated with the aza-enolate **49**, generating **50**, together with 32% of recovered starting material (11:1; **47**/**48**). Treatment of **50** with sulfuric acid afforded the indole **52** as a mixture (4:3, cis/trans), together with the byproduct **51**. After basic deprotection of **52**, (−)-*cis*-trikentrin A and (−)-*trans*-trikentrin A were obtained in 52% and 37% yield, respectively (Scheme 11). The synthesized trikentrins (6*S*,8*R*)-*cis*-trikentrin A ($[\alpha]_D$ −68.6 (*c* 1.03, $CHCl_3$)) and (6*R*,8*R*)-*trans*-trikentrin A ($[\alpha]_D$ −26.8 (*c* 0.68, $CHCl_3$)) are levorotatory. Thus, the absolute configuration of the dextrorotatory[7] natural products could be assigned as (6*R*,8*S*)-*cis*-trikentrin A and (6*S*,8*S*)-*trans*-trikentrin A.

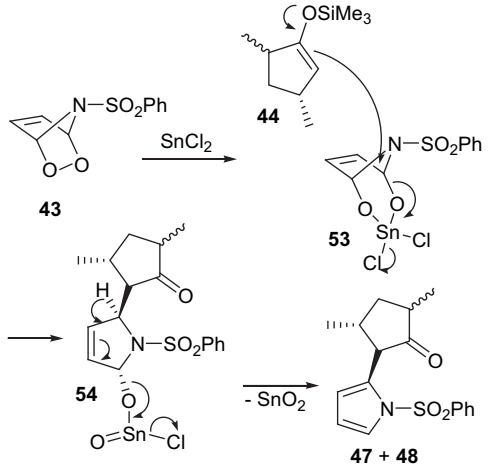


Scheme 11. Reagents and conditions: (a) $KMnO_4$; (b) (i) H^+, MeOH; (ii) $NaNH_2$; (c) (i) NaOMe, MeOH, −18 °C, 1 h; (ii) MeI, −18 °C, 14.5 h; (d) 47% HBr, 120 °C, 6 h; (e) LDA, THF, TMSCl, −80 °C, 15 min; (f) $SnCl_2$, EtOAc, −40 °C to −47 °C, 1 h, rt, 1.5 h; (g) toluene/Et_2O (1:1), −75 °C to −65 °C, 1 h; (h) H_2SO_4 6.5%, 2-propanol, reflux, 14 h; (i) KOH 20% in DME/MeOH/H_2O (1:1:1), 85–90 °C, 6.5 h.

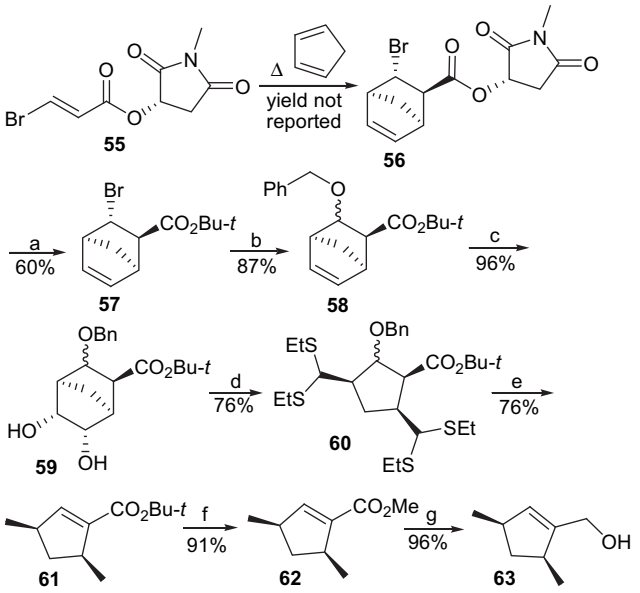
The proposed mechanism for the reaction of the enol ether **44** with compound **43** is summarized in Scheme 12. The first step would be the formation of organotin compound **53**, which would be attacked by the silyl enol ether **44**, generating the intermediate **54**. Elimination with aromatization and loss of SnO_2 would form the mixture of diastereoisomers **47** and **48**.

The same research group published the asymmetric synthesis of three other trikentrins,[15,22] assigning their absolute configurations. All syntheses used (3*R*,5*S*)-dimethycyclopentene **63**, as starting material, which was prepared in eight steps. The first one was a Diels–Alder reaction with the chiral non-racemic dienophile **55**. The Diels–Alder adduct **56** was transesterificated, giving **57**. The bromine atom was substituted by a benzyloxyl group, followed by a dihydroxylation with OsO_4, leading to **59**. In presence of $NaIO_4$, the diol was cleaved and afforded a dialdehyde, which was transformed into the corresponding thioketal **60**. Reductive desulphurization with Raney nickel followed by elimination promoted by *t*-BuOK led to the α,β-unsaturated ester **61**. The reduction of the ester moiety of **61** was tested with several hydrides and no success was achieved. Therefore, a transesterification with MeOH was necessary, giving **62**. Reduction of the ester group of **62** with DIBAL-H afforded **63** (Scheme 13).

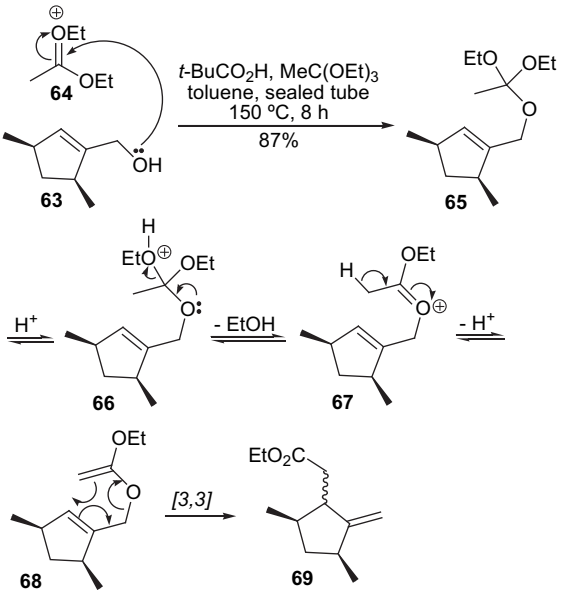
The synthetic sequence goes on transforming the alcohol **63** into the olefin **69** via a Claisen rearrangement. In the presence of pivalic acid, 1,1,1-triethoxyethane leads to **64**, which is attacked by the allylic alcohol **63**, affording the ortho ester **65**. After protonation, **66** is formed and another ethanol molecule is eliminated, leading to **67**. The diene **68** is generated by a proton loss and undergoes a [3,3]-sigmatropic rearrangement affording the unsaturated ester **69** (Scheme 14).



Scheme 12.

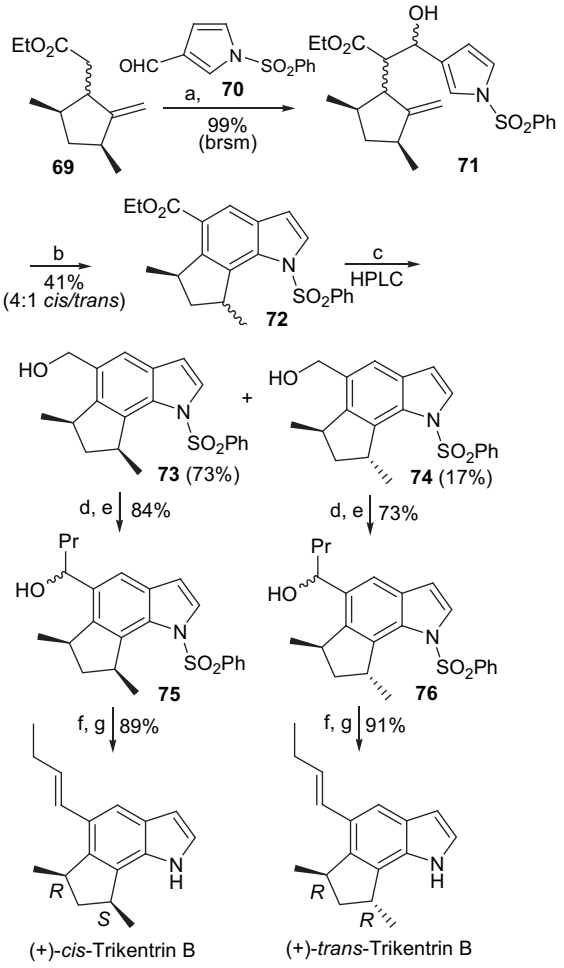


Scheme 13. Reagents and conditions: (a) (i) NaOH, DME, MeOH, 0 °C, 1 h; (ii) CH_2Cl_2, H_2SO_4, isobutene, −20 °C, 2 h and rt, 48 h; (b) (i) NaH, benzylic alcohol, THF, 0 °C, 20 min; (ii) 0 °C, 3 h; (c) OsO_4, triethylamine *N*-oxide, rt, 15 h; (d) (i) $NaIO_4$, THF, H_2O, 0 °C, 1 h; (ii) CH_2Cl_2, EtSH, $BF_3{\cdot}Et_2O$, 0 °C, 18 h; (e) (i) Raney nickel W-2, DME, reflux, 2 h; (ii) THF, *t*-BuOK, 0 °C, 1 h; (f) H_2SO_4, MeOH, reflux, 3 h; (g) DIBAL, hexane, −65 °C.



Scheme 14.

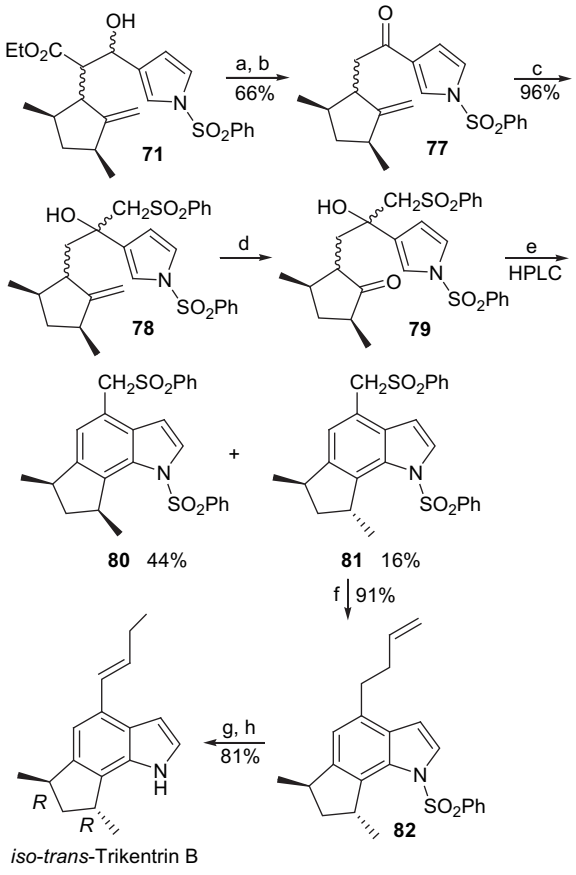
The enolate of the ester **69** underwent a nucleophilic addition to formyl pyrrole **70**, leading to **71**. Oxidative cleavage of the exocyclic double bond of **71** with catalytic OsO_4 and $NaIO_4$ led to the corresponding ketone. The subsequent acid-promoted cyclization afforded a mixture of indoles (**72**). After HPLC and reduction of the ester group of **72**, alcohols **73** and **74** were obtained in 73% and 17% yield, respectively. The oxidation of the primary alcohol with MnO_2 followed by a nucleophilic addition of the resulting aldehyde with *n*-propylmagnesium bromide converted **73** into **75**. This secondary alcohol was dehydrated with *p*-toluene sulfonic acid and the nitrogen was deprotected forming (6*R*,8*S*)-(+)-*cis*-trikentrin B ($[\alpha]_D$ +102 (*c* 0.18, $CHCl_3$)). The same reaction sequence was repeated from **74**, affording (6*R*,8*R*)-(+)-*trans*-trikentrin B ($[\alpha]_D$ +24.3 (*c* 0.078, $CHCl_3$)) (Scheme 15). Direct comparison of the value of $[\alpha]_D$ of (6*R*,8*R*)-(+)-*trans*-trikentrin B with that of natural product ($[\alpha]_D$ −13 (*c* 1.97, $CHCl_3$))[7] made possible to assign its absolute configuration as (6*S*,8*S*)-*trans*-trikentrin B. The same comparison was not possible to (6*R*,8*S*)-*cis*-trikentrin B because the natural product was isolated as a 3:2 mixture with the *iso*-*trans*-trikentrin B isomer.



Scheme 15. Reagents and conditions: (a) (i) LDA, THF, −68 °C, 40 min; (ii) −78 °C, 40 min; (b) (i) OsO_4, $NaIO_4$, THF, H_2O, rt, 18 h; (ii) PTSA, PhSH, reflux, 4 h; (c) $LiAlH_4$, THF, −20 °C, 10 min, 0 °C, 2 h; (d) MnO_2, CH_2Cl_2, rt, 1.5 h; (e) *n*-PrMgBr, THF, −20 °C, 20 min; (f) C_6H_6, PTSA, reflux, 0.5 h; (g) KOH, DME/MeOH/H_2O (1:1:1), reflux, 3 h.

In the same paper, the synthesis of (6*R*,8*R*)-*iso*-*trans*-trikentrin B is also described, following a reaction sequence similar to that shown in Scheme 15. Thus, intermediate **71** was converted into **77** by oxidation of the secondary alcohol followed by decarboxylation of the ester group. When treated with the organolithium, **77** led to ketone **79**, after oxidative cleavage of the exocyclic double bond of **78**. The intermediate **79** underwent an acid-mediated cyclization, leading to **80** and **81**, in 44% and 16% yield, respectively, after separation by HPLC. The trans isomer **81** reacted with allyltrimethylsilane, affording the indole **82**, which reacted with $RhCl_3$, that mediates the required double bond isomerization. Deprotection under basic conditions led to (6*R*,8*R*)-*iso*-*trans*-trikentrin B (ca. $[\alpha]_D$ 0 (*c* 0.11, $CHCl_3$)) (Scheme 16).

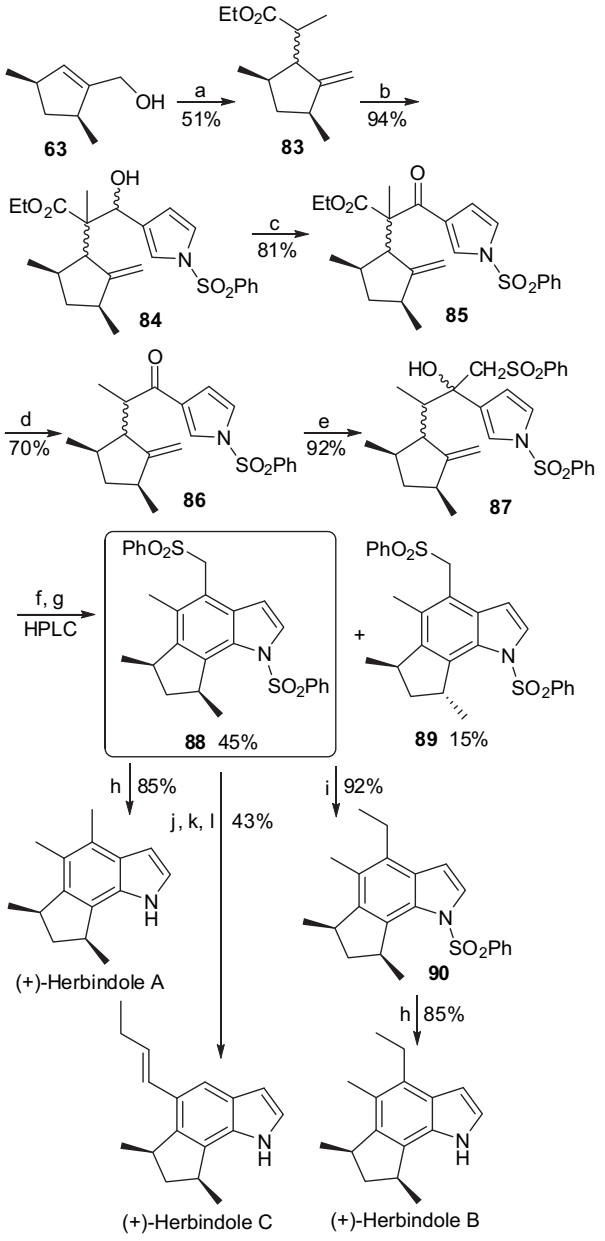
Having on hands the synthesized compounds (6*R*,8*R*)-iso-*trans*-trikentrin B and (6*R*,8*S*)-(+)-*cis*-trikentrin B, as well as a sample of the mixture of both isolated by Capon and his group, Kanematsu and co-workers could measure the circular dichroism of the natural mixture and the synthesized one. As there was not superposition of the graphics, theoretical graphics were constructed for various combinations of both molecules (synthesized enantiomers, opposite ones, and all possible combinations). The best superposition



Scheme 16. Reagents and conditions: (a) MnO_2, reflux, 2 h; (b) (i) NaOH, DME/MeOH/H_2O (1:2:1), reflux, 3 h; (ii) $PhSO_2Cl$, THF, DMF, NaH, 0 °C, 2 h; (c) $PhSO_2CH_2Li$, THF, BuLi, −73 °C, 20 min, −20 °C, 30 min; (d) OsO_4, $NaIO_4$, THF, H_2O, rt, 19 h; (e) $PhCH_2SH$, PTSA, reflux, 1.5 h; (f) allylTMS, $EtAlCl_2$, CH_2Cl_2, −20 °C; (g) EtOH, $RhCl_3$, sealed tube, 100 °C, 50 h; (h) KOH, DME/MeOH/H_2O (1:1:1), reflux, 3 h.

was obtained with the graphic of the mixture made by (6*S*,8*S*)-*iso-trans*-trikentrin B (opposite configuration when compared to the synthesized molecule) and (6*R*,8*S*)-*cis*-trikentrin B. Based on these results, the absolute configuration of these alkaloids was suggested.

The strategy used in the synthesis of trikentrins was applied in the enantioselective syntheses of herbindoles.[15,26] Claisen rearrangement of **63** afforded intermediate **83**, as previously discussed (Scheme 14). An enolization and subsequent nucleophilic addition to the pyrrole derivative **70** afforded alcohol **84**, which was oxidized to the keto ester **85**. This compound reacted with LiCl in HMPA leading to the loss of the ester group and formation of the intermediate **86**. Reaction of **86** with $PhSO_2CH_2Li$ led to alcohol **87**. An oxidative cleavage of the exocyclic double bond with OsO_4 followed by acid-mediated cyclization generated the tricyclic indoles **88** and **89**. After HPLC separation, the isomers **88** and **89** were obtained in 45% and 15% yield, respectively. As the relative configuration of the methyl groups of herbindoles is cis, **88** was used as a common intermediate for the preparation of all of these alkaloids (Scheme 17). The reduction of the phenyl sulfonyl mediated by metallic Mg and concomitant nitrogen deprotection afforded (+)-herbindole A ($[\alpha]_D$ +56.9 (*c* 0.28, $CHCl_3$)). A benzylic substitution with $AlMe_3$ converted **88** into **90**, which was deprotected with metallic Mg, furnishing (+)-herbindole B ($[\alpha]_D$ +51.2 (*c* 0.26, $CHCl_3$)). Finally, (+)-herbindole C ($[\alpha]_D$ +19.9 (*c* 0.18, $CHCl_3$)) was obtained from **88** by alkylation with allyltrimethylsilane followed by double bond isomerization and deprotection. The absolute configuration of herbindoles was assigned comparing the optical rotation of synthetic (+)-herbindole A to a sample of the natural alkaloid, which is levorotatory. Thus, natural herbindole A is (6*S*,8*R*). Assuming that all herbindoles would have the same biosynthetic route, the configuration of herbindoles B and C would also be (6*S*,8*R*).



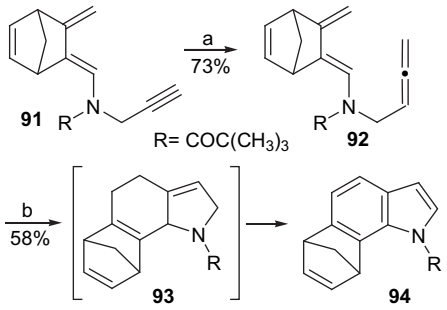
Scheme 17. Reagents and conditions: (a) $EtC(OEt)_3$, *t*-$BuCO_2H$, toluene, reflux, 3 h; (b) (i) LDA, THF, −65 °C, 40 min; (ii) **70**, −78 °C, 40 min; (c) MnO_2, CH_2Cl_2, rt, 1.5 h; (d) LiCl, HMPA/H_2O, 130 °C, 24 h; (e) $PhSO_2CH_2Li$, THF, BuLi, −73 °C, 20 min, −20 °C, 30 min; (f) OsO_4, $NaIO_4$, THF, H_2O, rt, 19 h; (g) PTSA, PhSH, toluene, reflux 5 h; (h) Mg, NH_4Cl, MeOH, rt, 2 h; (i) $AlMe_3$, CH_2Cl_2, 0 °C, 1 h; (j) allyltrimethylsilane, $EtAlCl_2$, CH_2Cl_2, −20 °C, 20 min; (k) RhI_3, EtOH, 100 °C, 50 h; (l) KOH, DME/MeOH/H_2O (1:1:1), reflux, 6 h.

Natsume and co-workers also reported the racemic synthesis of all trikentrins. Considering that the methods were similar to the asymmetric routes described above, the racemic works are not described in this review.[13] In summary, Natsume and co-workers accomplished the synthesis of several trikentrins and herbindols, assigning their absolute configuration. A key reaction in this comprehensive and hard work is a pyrrole indolization reaction.

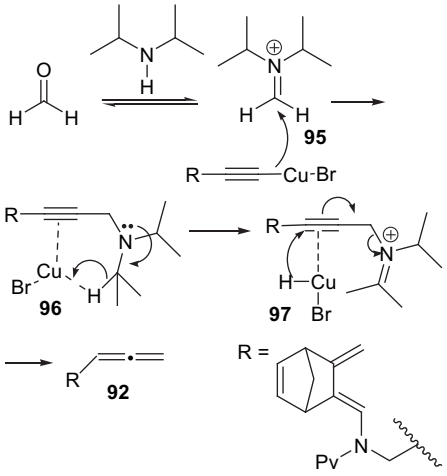
2.3. Syntheses of Kanematsu and co-workers

In 1986, Kanematsu and Yasukouchi studied the construction of the tricyclic backbone of trikentrins by an intramolecular Diels–

Alder reaction of an allenic dienamide (Scheme 18).[35] The preparation of the allene follows the Crabbé homologation protocol (Scheme 19).[36–39] Formaldehyde would react with di-isopropylamine to produce the iminium **95**. This intermediate would be attacked by the alkynylcopper (formed from the alkyne and CuBr) leading to **96**. This compound would lead to the iminium **97**, which subsequently would undergo to a [1,5]-sigmatropic rearrangement of hydrogen furnishing the desired allene **92**.

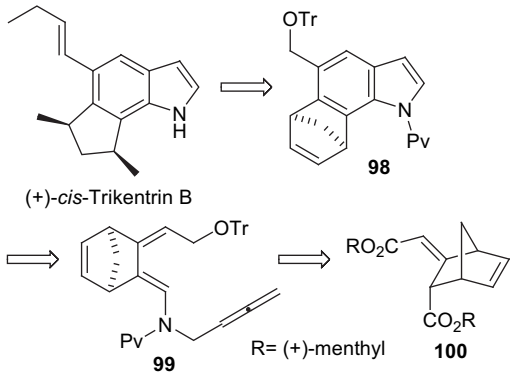


Scheme 18. Reagents and conditions: (a) HCHO, *i*-Pr_2NH, CuBr, dioxane, 101 °C, 5 h; (b) chloroanil, toluene, 110 °C.



Scheme 19.

The racemic and asymmetric total synthesis of *cis*-trikentrin B was accomplished using the above-mentioned strategy.[21] The target molecule would be prepared from compound **98** through oxidative cleavage followed by functional group transformations, which would deliver the groups in the cyclopentane ring with the required stereochemistry. Moreover, the side chain would also be installed from **98**. The requisite cyclic arrangement of **98** would be constructed by an intramolecular Diels–Alder reaction of **99**, that could be prepared from the norbornene derivative **100** (Scheme 20).



Scheme 20.

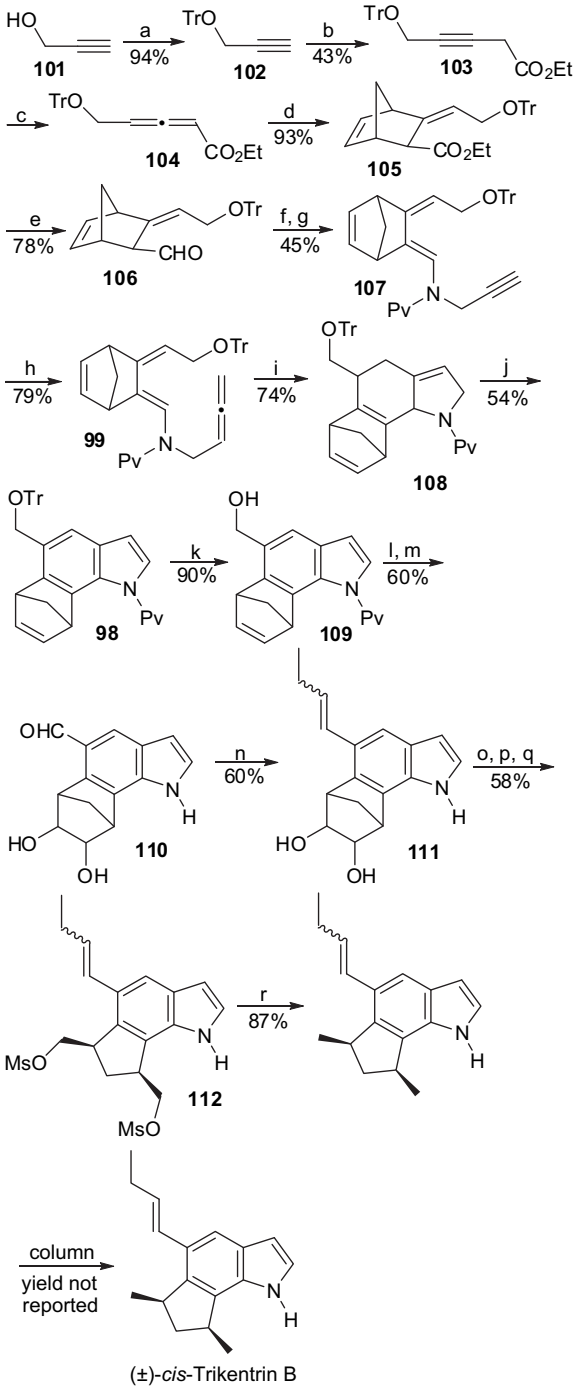
From propargylic alcohol (**101**), the allene **104** was prepared, affording adduct **105** after a Diels–Alder reaction with cyclopentadiene. The reduction of the ester group led to the corresponding alcohol, which was oxidized to the aldehyde **106**. Treating the aldehyde **106** with propargylamine followed by reaction with pivaloyl chloride led to **107**. Analogously to the model study, reacting **107** with formaldehyde, di-isopropylamine, and a catalytic amount of CuBr led to the allenic dienamide **99**. When heated to 160 °C, the intramolecular Diels–Alder reaction afforded adduct **108**, in 74% yield, which was subsequently aromatized to give **98**. Alcohol **109** was obtained from **98** by deprotection. Oxidation of the resulting alcohol to aldehyde and dihydroxylation with OsO_4 of the double bond gave the diol **110**. A Wittig olefination of **110** afforded a 2:1 mixture of the *E*/*Z* isomers of **111**. This diol mixture underwent an oxidative cleavage with $NaIO_4$ leading to the corresponding *cis*-aldehyde. Reduction with DIBAL followed by mesylation of the formed diol led to **112**. The reduction of **112** was accomplished using NaI and Zn according to Fujimoto's method,[40] forming (±)-*cis*-trikentrin B as a 2:1 mixture of *E*/*Z* isomers, in 87% yield. The isomers were separated by a silica gel column chromatography affording (±)-*cis*-trikentrin B in a pure form. The yield for this purification step was not reported (Scheme 21).

This methodology was further used in 1996 by the same research group in the enantioselective synthesis of (+)-*cis*-trikentrin B.[23] A five-step sequence formed the optically active bicycle **100**, used as starting material.[41] The authors did not report the yields of steps (a)–(d).[21] The diacid **115** was formed from methyl 3-oxopentanedioate (**113**) by treatment with phosphorus pentachloride followed by hydrolysis with HCl. An esterification of diacid **115** with (+)-menthol afforded diester **116**, as a 6:1 *E*/*Z* mixture, as determined by NMR. A dehydrochlorination of **116** with Et_3N led to allene **117**, after recrystallization. The Diels–Alder reaction of allene **117** with cyclopentadiene formed the adduct **100**, in 89% yield (Scheme 22).

The reduction of adduct **100** led to the diol **118**,[42] which was selectively oxidized at the allylic position affording the corresponding carboxylic acid. The remaining hydroxyl group allowed an intramolecular cyclization to form the tricyclic lactone **119**. This intermediate underwent a base-mediated hydrolysis followed by an esterification leading to the hydroxyl ester **120**.[43] Functional group modifications converted **120** into **122**. Once oxidized, the intermediate **122** yielded an aldehyde, which was treated with propargylamine, forming an enamine, which was protected with pivaloyl group, generating **107**. The optically active allene **99**, obtained from homologative allenylation of **107**, was heated to 160 °C in toluene forming the tetracycle **123** by intramolecular Diels–Alder reaction. A subsequent aromatization reaction gave the indole (+)-**98**. A dihydroxylation mediated by a catalytic amount of OsO_4 and an oxidative cleavage with sodium periodate afforded dialdehyde **124**. This compound was reduced to the corresponding alkane in three steps (reduction to alcohol, mesylation, and mesylate reduction) leading to (+)-**126**. Three more steps (pyrrole protection, deprotection, and alcohol oxidation) afforded aldehyde (+)-**127**. A subsequent nucleophilic addition of *n*-propylmagnesium bromide followed by elimination of the benzylic acid with PTSA and indole deprotection with $NaBH_4$ led to (6*R*,8*S*)-(+)-*cis*-trikentrin B ($[\alpha]_D$ +100.2 (*c* 0.5, $CHCl_3$)) (Scheme 23). In conclusion, Kanematsu and co-workers accomplished the racemic and the asymmetric syntheses of *cis*-trikentrin B using as key reaction an intramolecular Diels–Alder cycloaddition of an allenic dienamide.

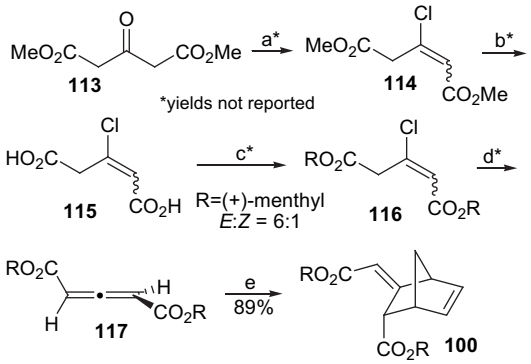
2.4. Syntheses of Boger and co-workers

In some studies on heteroaromatic Diels–Alder reactions, Boger and co-workers observed indole formation from sulfurylated symmetric tetrazines.[44] In 1991, Boger and Zhang published the



Scheme 21. Reagents and conditions: (a) TrCl, Et_3N, CH_2Cl_2; (b) *n*-BuLi, THF, −78 °C, 30 min; $BF_3{\cdot}Et_2O$, −78 °C to −20 °C; N_2CHCO_2Et, −20 °C, 1 h; (c) Et_3N, $CHCl_3$, rt, 7 h; (d) cyclopentadiene, C_6H_6, 80 °C, 3 h; (e) (i) $LiAlH_4$, THF, 0 °C, 1 h; (ii) PCC, CH_2Cl_2, 30 min; (f) propargylamine, MS 4 Å, Et_2O; (g) (i) NaH, −18 °C, 10 min; (ii) *t*-BuCOCl, −18 °C to rt; (h) HCHO, *i*-Pr_2NH, CuBr, dioxane, 101 °C, 5 h; (i) toluene, 160 °C, 2 h; (j) chloroanyl, toluene, 110 °C; (k) camphorsulfonic acid, MeOH, THF, rt, 10 h; (l) PCC, CH_2Cl_2; (m) OsO_4, NMO, dioxane/H_2O, rt, 10 h; NaOH, MeOH, H_2O, rt, 5 min; (n) $Ph_3P{=}CHEt$, THF, 0 °C to rt; (o) $NaIO_4$, THF, H_2O, rt, 5 h; (p) DIBAL, toluene, −78 °C, 30 min; (q) MsCl, NEt_3, CH_2Cl_2, 0 °C, 30 min; (r) Zn, NaI, DME, 20 h.

total synthesis of (±)-*cis*- and (±)-*trans*-trikentrin A using this reaction.[14] Thus, *cis*-trikentrin A would be obtained from the allene **128** by an intramolecular Diels–Alder reaction, when would occur the formation of the indole ring. Compound **128** would be synthesized from diazine **129** and allene **130**. Diazine **129** would be prepared from enamine **131** and tetrazine **132**, also by a Diels–Alder cycloaddition (Scheme 24). The strategy toward (±)-*trans*-trikentrin



Scheme 22. Reagents and conditions: (a) PCl_5; (b) 20% HCl, reflux; (c) (+)-menthol, H_2SO_4, C_6H_6, reflux; (d) Et_3N, THF, 0 °C, recryst in pentane; (e) cyclopentadiene, $AlCl_3$, CH_2Cl_2, −78 °C, 3 h.

A is based on the epimerization of **135**, which would be prepared from **129**, to its trans isomer **134**. The other steps would be analogous to the synthesis of *cis*-trikentrin A (Scheme 25).

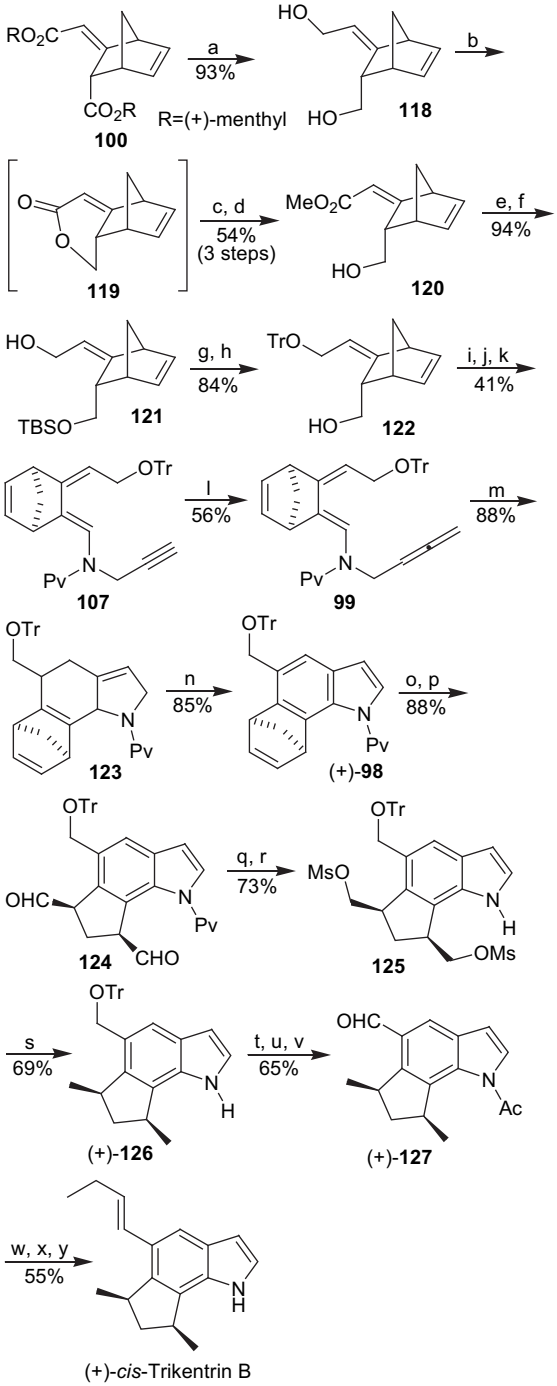
In the synthesis of (±)-*cis*-trikentrin A, the starting 2,4-dimethylcyclopentanone was converted into enamine **131** (*cis*/*trans*=3:1). This compound was treated with tetrazine **132** affording **136**, in a diastereoselective fashion. The loss of molecular nitrogen, which is thermodynamically favored, is the driving force, allowing mild reaction conditions to be used. Elimination of pyrrolidine under acid conditions led to diazine **129**, in 85% yield calculated from **132** (Scheme 26). The authors explain the high diastereoselectivity of the Diels–Alder reaction through the transition states **137** and **138**, achieved from trans and cis isomer, respectively. In **137**, there is a steric hindrance in both faces of the dienophile, which prevents the approach of the reagent. In **138**, a less hindered face favors that approach (Fig. 3).

The methylsulfide groups from **129** were oxidized to methane sulfonates using *m*-CPBA affording intermediate **135**. This compound was treated with allenic amine **130**, giving **128**. Nitrogen protection and intramolecular Diels–Alder reaction of **128** yielded the indole **107**. The acetyl group of **139** was removed with LiOH leading to (±)-*cis*-trikentrin A (Scheme 27).

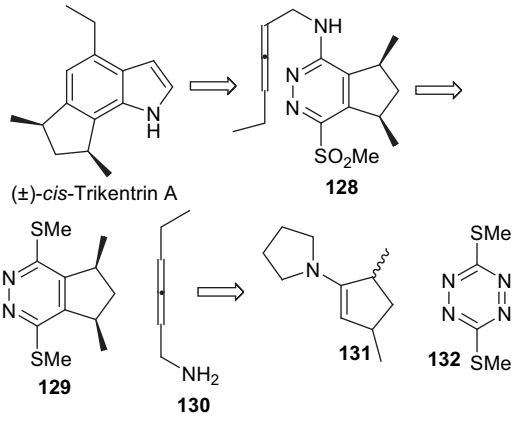
The synthesis of (±)-*trans*-trikentrin A was accomplished from intermediate **135**, which has *cis* methyl groups. This compound was epimerized in a basic medium giving **134** in 40% yield and 55% of recovered starting material after separation by flash chromatography. The sequence used in the synthesis of (±)-*cis*-trikentrin A synthesis was applied to **134**, affording the natural product (Scheme 28). Thus, Boger and Zhang accomplished a short and convergent total synthesis of *cis*- and of *trans*-trikentrin A using as key transformation heteroaromatic Diels–Alder reactions. The synthesis of *cis*-trikentrin A is highly selective in the formation of the *cis*-1,3-dimethylcyclopentanic moiety.

2.5. Synthesis of Blechert and co-workers

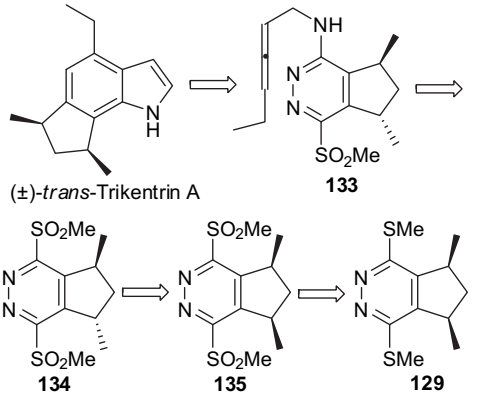
In 1995, Blechert and co-workers accomplished the total synthesis of (±)-*cis*-trikentrin A.[16] Two routes were investigated. In the first, *cis*-trikentrin A would be obtained from the indanone derivative **141**, which would be prepared from **142** by the intramolecular Friedel–Crafts acylation. The indole would be prepared from the functionalized benzene **142** (Scheme 29). In the second and effective approach the order of formation of the indole and of the cyclopentane rings are inverted, when compared to the first route. Thus, the target molecule would be prepared from the nitro indane **144** using a Bartoli reaction to construct the indole ring. The five-membered ring of **144** would be installed by an intramolecular Heck coupling of **145**. Finally, **145** would be prepared from the functionalized benzene **146** (Scheme 30).



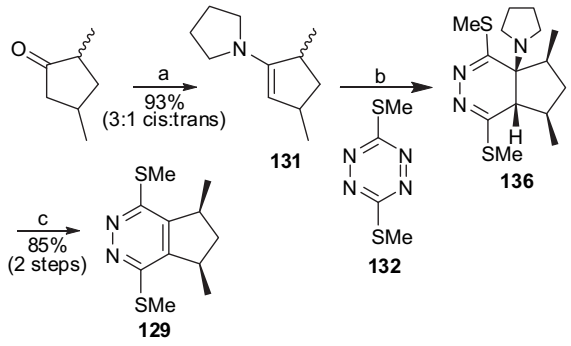
Scheme 23. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C to 0 °C;[42] (b) Ag_2CO_3, Celite, benzene, reflux; (c) LiOH, THF, H_2O; (d) $TMSCHN_2$, MeOH, benzene; (e) TBDMSCl, imidazole, DMAP, CH_2Cl_2; (f) DIBAL, CH_2Cl_2, −78 °C; (g) TrCl, Et_3N, DMAP, CH_2Cl_2; (h) TBAF, THF; (i) PCC, CH_2Cl_2; (j) propargylamine, MS 4 Å, Et_2O; (k) pivaloyl chloride, 2,4,6-collidine, CH_2Cl_2, rt; (l) HCHO, *i*-Pr_2NH, CuBr, 1,4-dioxane, reflux; (m) toluene, 160 °C; (n) MnO_2, CH_2Cl_2, rt; (o) OsO_4, NMO, pyridine, Et_2O, 1,4-dioxane; (p) $NaIO_4$, THF, H_2O, rt; (q) $NaBH_4$, MeOH, rt; (r) MsCl, Et_3N, Et_2O, 0 °C; (s) Zn, NaI, DME, reflux; (t) CH_3COCl, NaH, 18-crown-6, THF, rt; (u) camphorsulfonic acid, MeOH, THF, rt; (v) MnO_2, CH_2Cl_2, rt; (w) *n*-PrMgBr, THF, −10 °C; (x) *p*-TsOH, benzene, 50 °C; (y) $NaBH_4$, MeOH, rt.



Scheme 24.



Scheme 25.



Scheme 26. Reagents and conditions: (a) pyrrolidine, C_6H_6, reflux; (b) C_6H_6, 0–25 °C, 1 h; (c) C_6H_6, AcOH, 25 °C, 10 h.

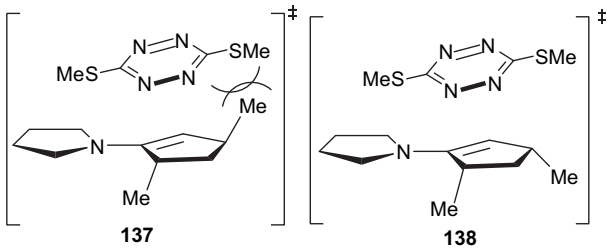
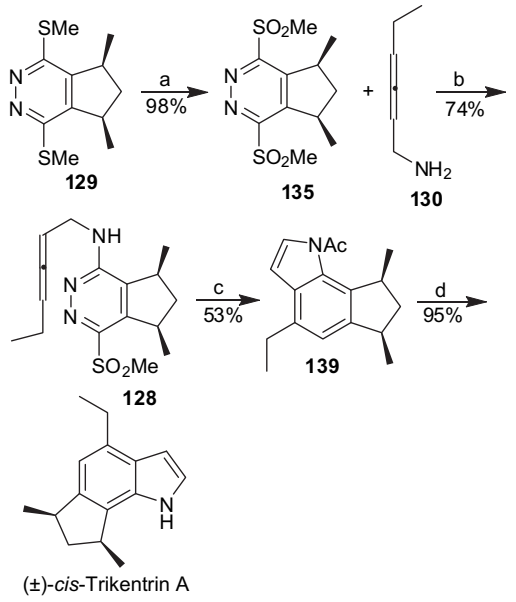
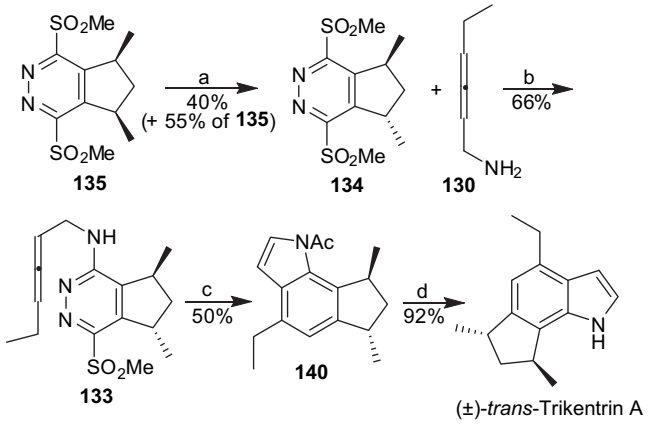


Figure 3. Possible transition states for the formation of **136**.

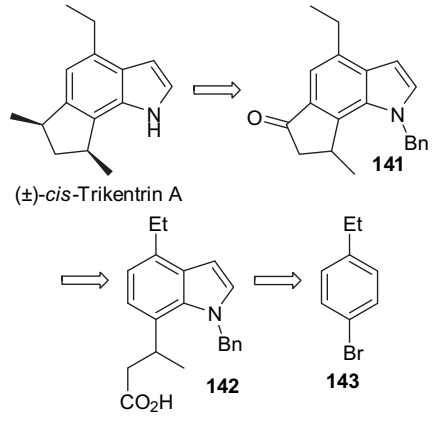
The first route began with nitration of 4-bromo-ethylbenzene (**143**) followed by Bartoli reaction leading to indole **147**. Protection of bromoindole **147** with benzyl bromide furnished **148**, which led to **142** after a Heck reaction with methyl crotonate. The reduction of the conjugated double bond with Mg/MeOH led to acid **142**. Attempts of intramolecular cyclizations of **142** afforded tricycle **149**, where the migration of the benzyl group to the C2 position was also observed (Scheme 31). Due to this undesirable result, this route was abandoned.



Scheme 27. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, −20 °C, 23 h; (b) CH_2Cl_2, 13 kbar, 25 °C, 4 days; (c) Ac_2O, NaOAc, 160 °C, 12 h; (d) LiOH, H_2O/MeOH/THF, 25 °C, 1 h.

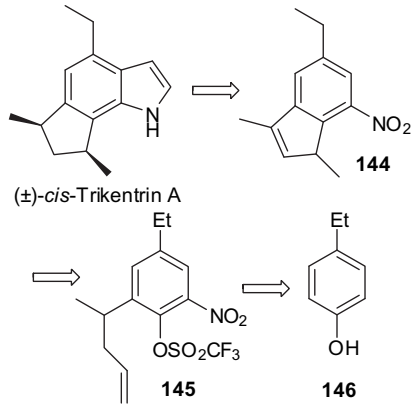


Scheme 28. Reagents and conditions: (a) Et_3N/THF, 65 °C, 60 h; (b) CH_2Cl_2, 13 kbar, 25 °C, 2 days; (c) Ac_2O, NaOAc, 160 °C, 11 h; (d) LiOH, H_2O/MeOH/THF, 25 °C, 1 h.

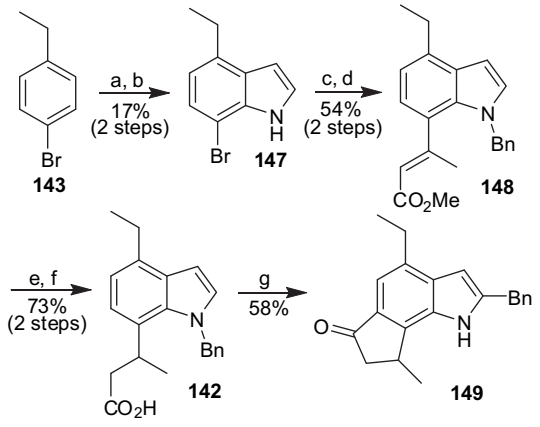


Scheme 29.

The Bartoli reaction used by Blechert to construct the indole ring was also applied in other syntheses (Schemes 54, 55, and 58). The proposed mechanism of Bartoli reaction[45] indicates that the first equivalent of Grignard reagent attacks an oxygen of nitro group, giving **151**. Steric reasons, due to the presence of an *ortho*-substituent (typically alkyl or halogen), may justify this attack. Loss of acetaldehyde from

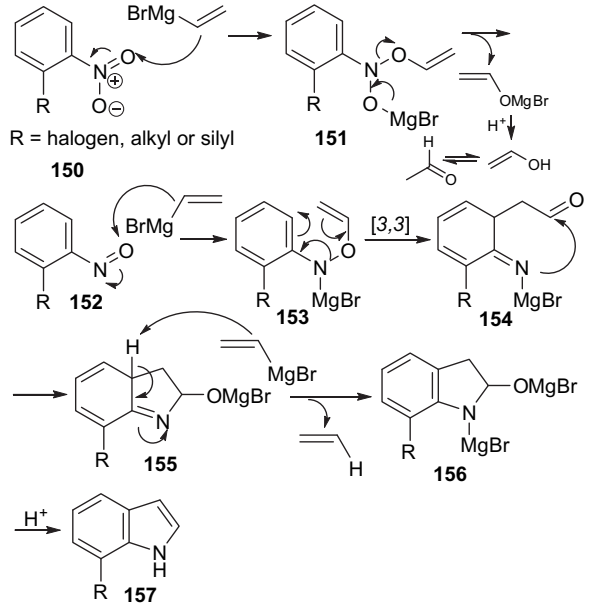


Scheme 30.



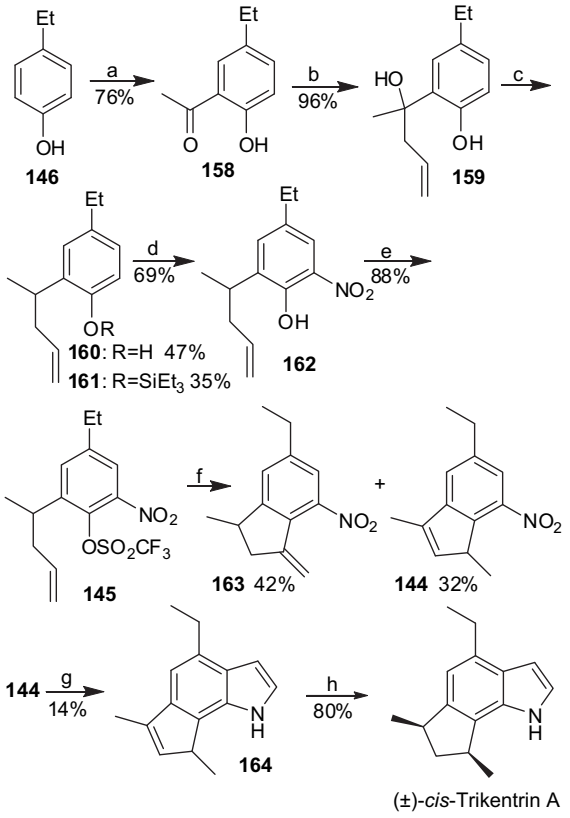
Scheme 31. Reagents and conditions: (a) 100% HNO_3, 0 °C, 3 h; (b) CH_2=CHMgBr, THF, −40 °C, 25 min; (c) (i) KOH, DMSO, rt, 1 h; (ii) BnBr, 0 °C; (d) methyl crotonate, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 115 °C, 14 h; (e) Mg, MeOH, 1.5 h; (f) KOH, *t*-BuOH, H_2O, 90 °C, 3.5 h; (g) polyphosphoric acid, 85 °C, 3.5 h.

intermediate **151** led to the nitroso compound **152**, which reacted with the second equivalent of vinylmagnesium bromide, affording the aminomagnesium **153**, through a 1,2-addition. This compound then underwent a [3,3]-sigmatropic rearrangement followed by ring closure leading to substituted indole **157** (Scheme 32).



Scheme 32.

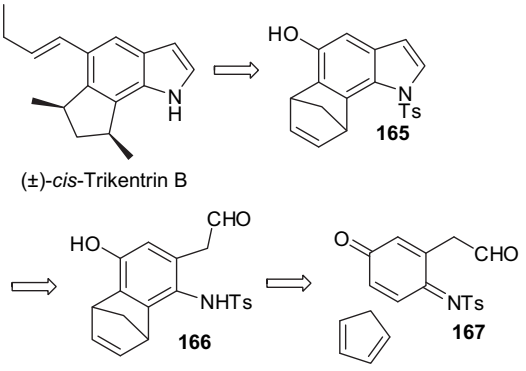
In the second approach of Blechert to synthesize (±)-*cis*-trikentrin A, the indane was first prepared by an intramolecular Heck reaction, followed by the construction of the indole moiety. The ethyl phenol **146** was transformed into the homoallylic alcohol **159**, through acylation followed by nucleophilic addition with allyl magnesium chloride. Reduction of benzylic alcohol with triethyl silane hydride afforded the desired product **160** and the silyl ether **161**. These compounds were nitrated giving the same products, which were grouped and purified together, leading to **162** in 69% yield. The phenol moiety of **162** was transformed into the corresponding triflate and submitted to an intramolecular Heck reaction affording isomers **163** and **144**. After a delicate chromatographic separation, the minor component **144** was indolized through a Bartoli reaction, generating **164**, in 14% yield. Hydrogenation of **164** was the last step to construction of the *cis*-dimethylcyclopentanic moiety, affording (±)-*cis*-trikentrin A. In conclusion, Blechert and his group reached (±)-*cis*-trikentrin A. Important reactions in this work are an intramolecular Heck coupling and a Bartoli reaction (Scheme 33).



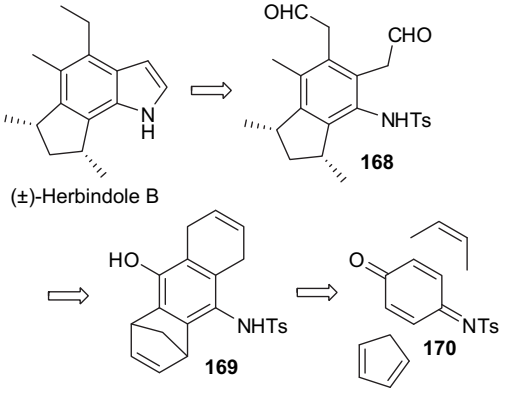
Scheme 33. Reagents and conditions: (a) (i) CH_3COCl, CF_3SO_3H (cat.), CH_2Cl_2, rt, 30 min; (ii) $AlCl_3$, 140 °C, 15 min; (b) CH_2=CHMgCl, THF, 0–65 °C, 25 min; (c) Et_3SiH, CF_3CO_2H, CH_2Cl_2, rt, 30 min; (d) HNO_3 65%, hexane (for **160**) or AcOH (for **161**), rt, 2 h; (e) $(CF_3SO_2)_2O$, 2,4,6-collidine, CH_2Cl_2, −20 °C, 2 h; (f) $Pd(OAc)_2$, PPh_3, Et_4NCl, Et_3N, CH_3CN, H_2O, rt to 50 °C, 1 h; (g) CH_2=CHMgBr, THF, −50 °C, 25 min; (h) H_2, Pd/C, MeOH.

2.6. Syntheses of Kerr and co-workers

In 2005, Kerr and co-workers published a total synthesis of *cis*-trikentrin B and of (±)-herbindole B. Their approach is based on the Diels–Alder of iminoquinones, such as **167** and **170**. However, a different starting material has been used for each natural product.[24] The strategy to construct the cyclopentyl moiety with cis stereochemistry between the methyl substituents is similar to that used in the syntheses of Kanematsu (Scheme 20),[21,23] i.e., the oxidative cleavage of the double bond of intermediates, such as **166** and **169** (Schemes 34 and 35) from the Diels–Alder adduct.

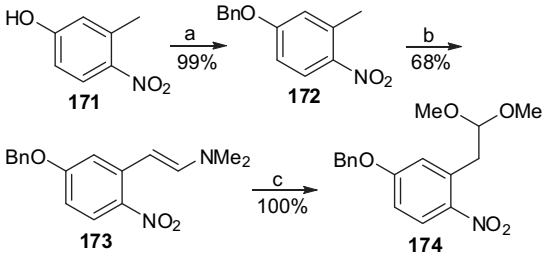


Scheme 34.



Scheme 35.

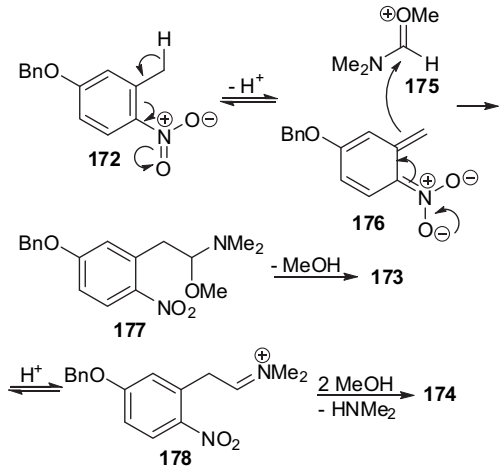
The synthesis of (±)-*cis*-trikentrin B required the preparation of the functionalized benzene **174**, which was obtained in four steps from *p*-nitrophenol **171** according to Todd's procedure (Scheme 36).[46]



Scheme 36. Reagents and conditions: (a) BnBr, Cs_2CO_3, DMF, rt, 16 h; (b) Me_2N-$CH(OMe)_2$, DMF, reflux, (c) camphorsulphonic acid, MeOH, reflux, 16 h.[46]

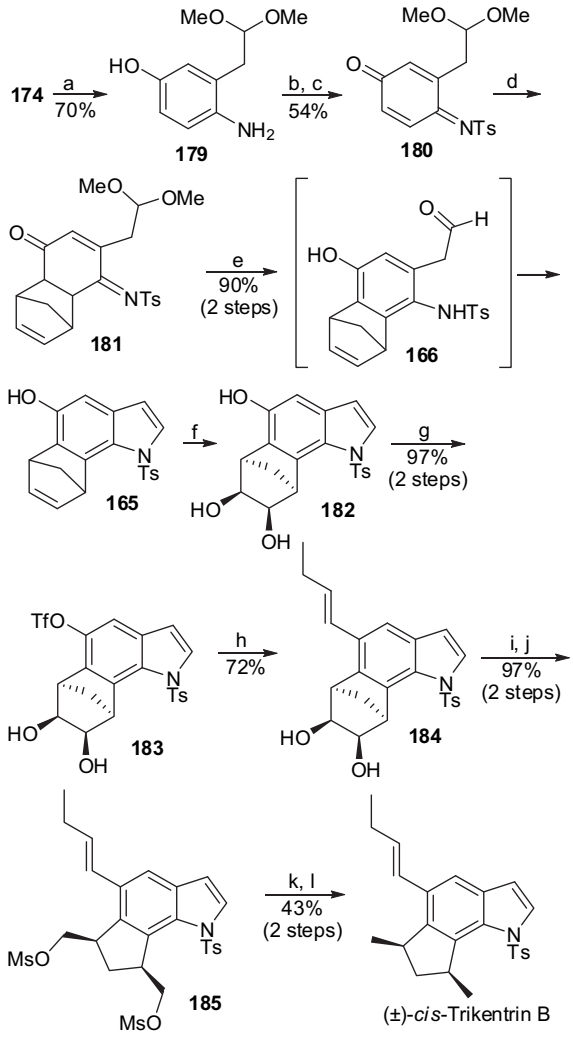
The mechanism proposed for the formation of **174** is shown in Scheme 37. A proton loss from the methyl group in **172** generates the intermediate **176**, which would attack the oxonium ion **175** (formed by a loss of MeOH from $Me_2NCH(OMe)_2$) leading to **177**. Without changes in reaction conditions, loss of MeOH from **177** would lead to the enamine **173**. The iminium **178** is generated from **173** under acidic conditions. The formation of **174** would take place when **178** would be attacked by two molecules of methanol with loss of the dimethylamine.

The synthesis of Kerr and his group goes on reducing the nitro group of compound **174** to the corresponding amino derivative **179**. After N-tosylation and oxidation with DIB (diacethoxy iodobenzene), the iminoquinone **180** reacted with cyclopentadiene

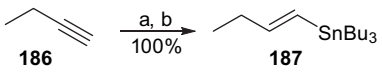


Scheme 37.

affording **181**. Treating this compound with HCl led to the aromatization, as well as ketal hydrolysis, generating the aldehyde **166**. An in situ cyclization was performed under these conditions leading to the tricyclic indole **165**. Dihydroxylation of the double bond led to diol **182**. Triflation of the phenol group of **182** led to **183**. The next step was a Stille coupling between the triflate **183** and the stannane **187** (quantitatively prepared in two steps from 1-butyne, Scheme 39), which resulted in diol **184**. This compound underwent an oxidative cleavage followed by reduction, giving a diol that was mesylated and reduced to the corresponding alkane. Deprotection of the nitrogen concluded the synthesis of (±)-*cis*-trikentrin B (Scheme 38).



Scheme 38. Reagents and conditions: (a) Pd/C, H_2, EtOH, rt, 2 h; (b) TsCl, pyridine; (c) DIB, CH_2Cl_2, 0 °C; (d) cyclopentadiene, CH_2Cl_2, 0 °C; (e) HCl, THF; (f) OsO_4, NMO, THF, H_2O; (g) Tf_2O, Et_3N, CH_2Cl_2, −78 °C; (h) **187**, $Pd(PPh_3)_2Cl_2$, LiCl, DMF, 140 °C; (i) (i) $NaIO_4$, THF, H_2O; (ii) $NaBH_4$, 0 °C; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C; (k) NaI, Zn, DME, reflux; (l) TBAF, THF, reflux.



Scheme 39. (a) (i) DIBAL, hexane, 50 °C; (ii) I_2, THF, −50 °C to rt; (b) (i) *t*-BuLi, Et_2O, −78 °C; (ii) Bu_3SnCl, Et_2O, −78 °C to rt.

The synthesis of herbindole B began with a Diels–Alder reaction between the iminoquinone **170** and the 1,3-butadiene. The adduct **188** was oxidized to compound **189**, which led to the tetracycle **190** after another Diels–Alder reaction, but this time with cyclopentadiene. The aromaticity was restored treating **190** with MeLi, which gave **169**. Triflation and chemoselective dihydroxylation of the benzonorbornenyl double bond gave the diol **191**. Protection of the diol, oxidative cleavage of the double bond, and cyclization reaction under acidic conditions gave the indole **193**. The ethyl group of the C4 position was achieved through reduction of the aldehyde to the corresponding alcohol, which was mesylated and reduced to the alkane, giving **194**. The triflate **194** was submitted to a Stille coupling with $SnMe_4$, which inserted the methyl group at C5 position. After deprotection of the diol, the reactions employed in the synthesis of herbindole B (Scheme 40) were similar to those used to obtain (±)-*cis*-trikentrin B (Scheme 38).

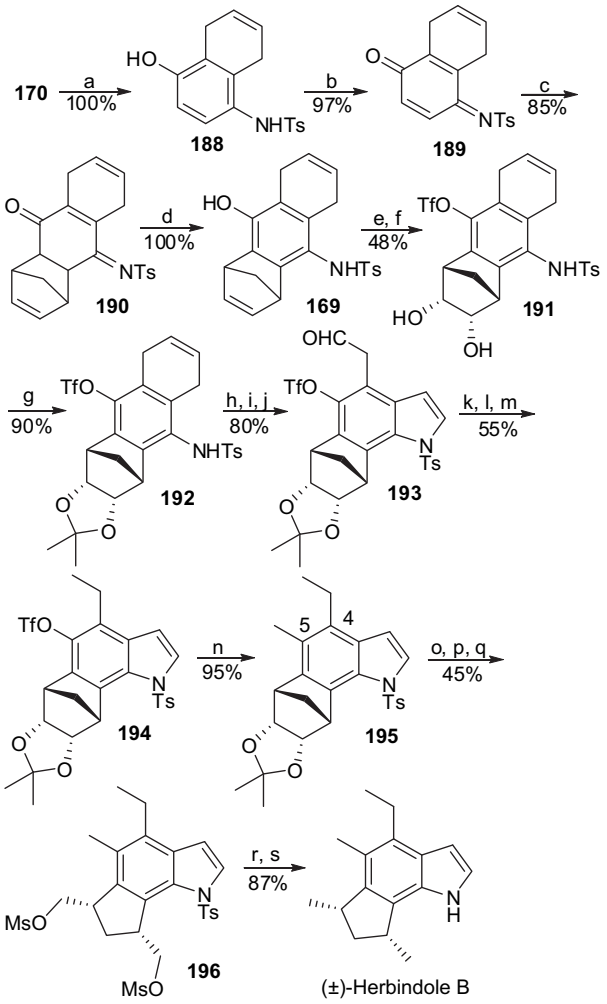
After 2 years, in 2007, the same research group published the total synthesis of (±)-*cis*-trikentrin A, (±)-herbindole A and again (±)-herbindole B employing the same strategy used in the syntheses of 2005.[18] The difference is that a common intermediate (**197**) connects the synthesis of the three alkaloids (Scheme 41).

For (±)-herbindole A, compound **182** was prepared as discussed in the synthesis of (±)-*cis*-trikentrin B (Scheme 38). The regioselective iodination of **182** led to the key intermediate **197**. Protection of the diol and triflation of the hydroxyl group gave **198**, which underwent a Stille coupling on both active sites (OTf and I), affording the dimethyl derivative **199**. From this intermediate, the synthesis is analogous to (±)-herbindole B (steps o–s in Scheme 40) leading to the natural product (Scheme 42).

The alkaloids (±)-*cis*-trikentrin A and (±)-herbindole B were both obtained from **194**, which was generated from **197**, in three steps. First, the diol moiety of **197** was protected, giving **200**, which was submitted to a coupling reaction with diethylzinc. After the ethyl group insertion, the hydroxyl group was transformed into a triflate affording **194**. The synthesis of (±)-herbindole B was accomplished from **194** by following the last six steps of the precedent synthesis described for this compound (Scheme 40, steps n–s). For the synthesis of (±)-*cis*-trikentrin A, the C–OTf bond of **194** was reduced with ammonium formate. Deprotection of the diol afforded **201**. From this intermediate, the last four steps employed in the synthesis of (±)-herbindole B were repeated (Scheme 40, steps p–s) and the desired natural product was obtained (Scheme 43). Thus, in summary, based on the Diels–Alder cycloaddition of iminoquinones, syntheses of herbindoles and *cis*-trikentrins were accomplished by Kerr and co-workers.

2.7. Syntheses of Funk and co-workers

In 2006, Funk and Huntley published the total synthesis of (±)-*cis*-trikentrin A and of (±)-*cis*-trikentrin B.[17] The six-membered ring of (±)-*cis*-trikentrin B would be constructed from **202** by an electrocyclic reaction. The intermediate **202** would be obtained by



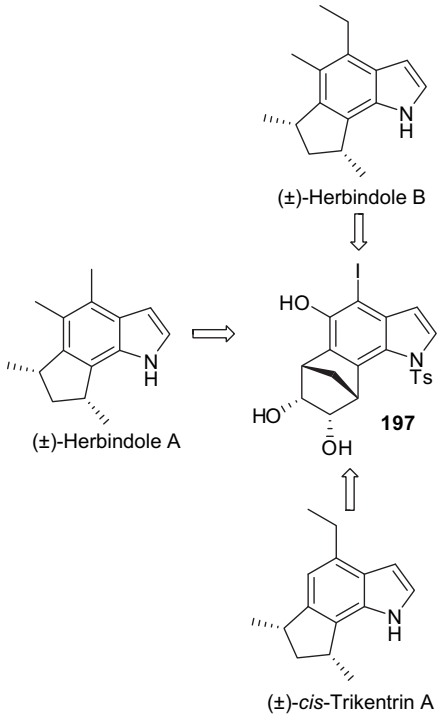
Scheme 40. Reagents and conditions: (a) (i) 1,3-butadiene, CH_2Cl_2, rt, 2 days; (ii) DBU, 0 °C; (b) $NaIO_4$, SiO_2, CH_2Cl_2; (c) cyclopentadiene, CH_2Cl_2, 0 °C; (d) MeLi, THF, −78 °C, H^+; (e) Tf_2NPh, NaH, THF; (f) OsO_4, NMO, THF, H_2O; (g) 2-methoxy-propene, PTSA, DMF; (h) OsO_4, NMO, THF, H_2O; (i) $NaIO_4$, THF, H_2O; (j) H_2SO_4, THF; (k) $NaBH_4$, MeOH, 0 °C; (l) MsCl, Et_3N, CH_2Cl_2, 0 °C; (m) NaI, Zn, DME, reflux; (n) $SnMe_4$, $Pd(PPh_3)_2Cl_2$, LiCl, DMF, 140 °C; (o) AcOH, reflux; (p) (i) $NaIO_4$, THF, H_2O; (ii) $NaBH_4$, 0 °C; (q) MsCl, Et_3N, CH_2Cl_2, 0 °C; (r) NaI, Zn, DME, reflux; (s) TBAF, THF, reflux.

the coupling of the five-membered ring fragments **203** and **204**, which would be prepared from the readily available starting materials **206** and **205**, respectively (Scheme 44). An analogous plan was used to synthesize (±)-*cis*-trikentrin A, but changing the fragment **204** to **208**, which could also be prepared from **205** (Scheme 45).

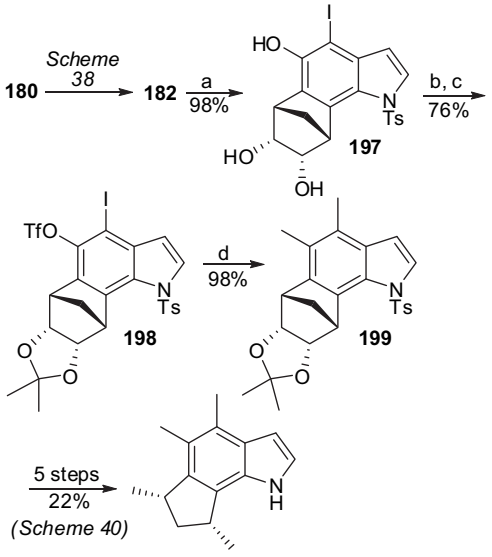
In the synthesis of (±)-*cis*-trikentrin B, the cyclopentanic triflate **203** was prepared in two steps from cyclopentanone **206** (Scheme 46). The first step is a rhodium catalyzed 1,2-hydrosilylation[47] followed by triflation, as described by Corey and co-workers.[48]

For the triflation of **209**, the authors proposed that trifluoromethanesulfonyl fluoride (TfF) is formed in the reaction mixture from $PhNTf_2$ and CsF. The TfF would be attacked by the enolate **210**, leading to the triflate **203**. The enolate **210** would be obtained from the cleavage of the O–Si bond promoted by another equivalent of CsF (Scheme 47).[48]

The stannane **204**, next fragment to be synthesized, was prepared in six steps from **205**.[49,50] First, the ketone of **205** was reduced and the corresponding alcohol was dehydrated, affording **211**. A Vilsmeier–Haack formylation of **211** followed by a Wittig reaction with the phosphorane **213** led to **214**. The reduction of the ester in **214** generated the corresponding alcohol, which was protected as the TIPS ether, yielding **215**. The stannane **204** was



Scheme 41.

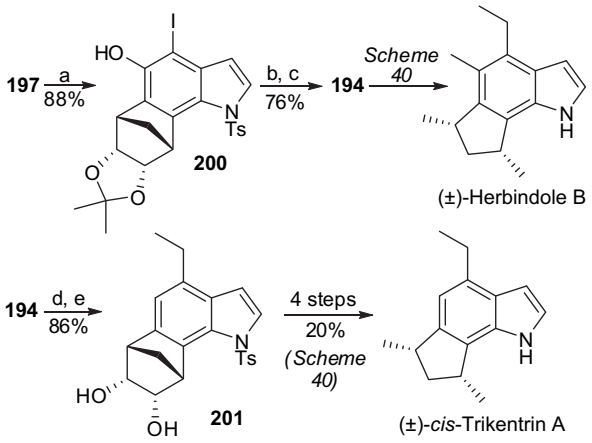


Scheme 42. Reagents and conditions: (a) NIS, THF, 0 °C; (b) 2-methoxy-propene, PTSA, DMF; (c) Tf_2NPh, NaH, THF; (d) $SnMe_4$, $Pd(PPh_3)_2Cl_2$, LiCl, DMF, 140 °C.

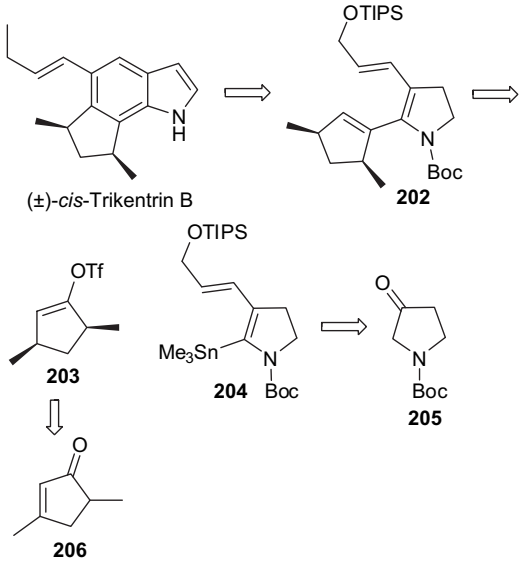
obtained from diene **215** through a metalation reaction followed by transmetalation (Scheme 48).

The Stille coupling between **203** and **204** generated the triene **202**, which underwent an electrocyclic ring closure after heating, affording the tricycle **216**. Oxidation by DDQ led to the aromatization, yielding the indolinic derivative **217**, which was further oxidized to indole **218**. After Grignard reaction of **218** with *n*-propylmagnesium chloride, followed by dehydration of the benzylic alcohol, **219** was isolated. Deprotection of the nitrogen of **219** gave (±)-*cis*-trikentrin B (Scheme 49).

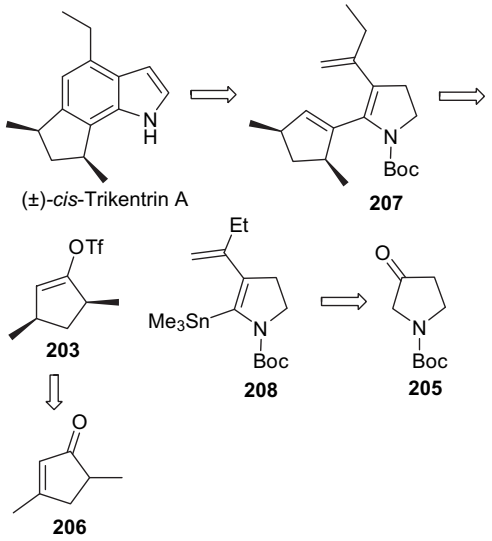
The synthesis of (±)-*cis*-trikentrin A was reached in nine steps from aldehyde **212**. The ketone **220** was produced after Grignard reaction of ethyl lithium and **212**, followed by oxidation of the



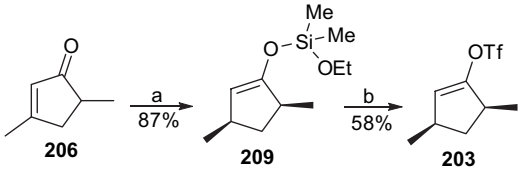
Scheme 43. Reagents and conditions: (a) 2-methoxy-propene, PTSA; (b) Et_2Zn, $Pd(dppf)Cl_2$, 1,4-dioxane, reflux; (c) Tf_2NPh, NaH, THF; (d) NH_4CHO_2, $Pd(PPh_3)_2Cl_2$, LiCl, DMF, 140 °C, sealed tube; (e) HCl, $MeOH/H_2O$, reflux.



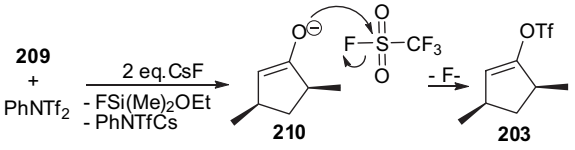
Scheme 44.



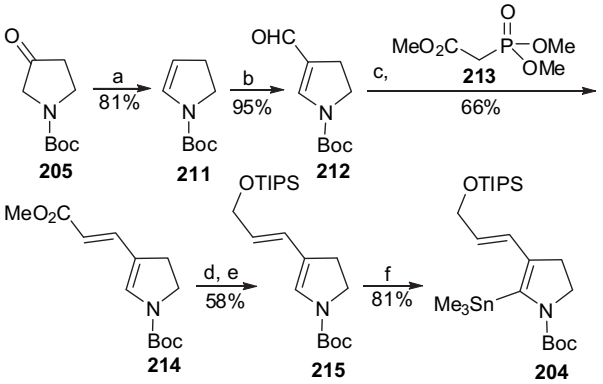
Scheme 45.



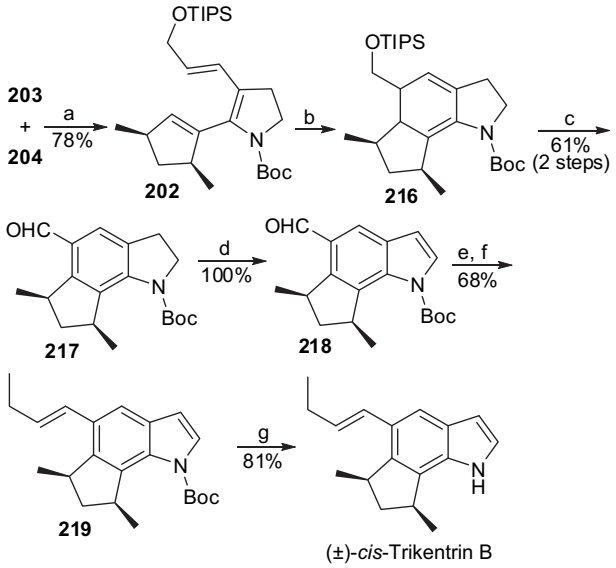
Scheme 46. Reagents and conditions: (a) 1.5 mol % [Rh(OH)(cod)], HMe_2SiOEt, −20 °C, 16 h; (b) $PhNTf_2$, CsF, DME, rt.



Scheme 47.



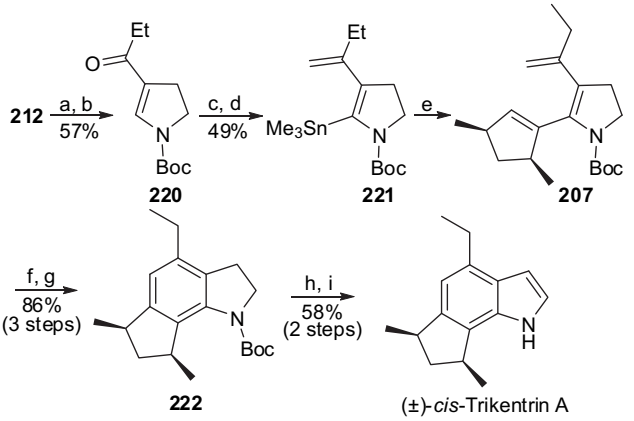
Scheme 48. Reagents and conditions: (a) (i) $LiBHEt_3$, toluene, −70 °C, 30 min;[49] (ii) TFAA, DPEA, DMAP, rt, 2 h; (b) oxalyl chloride, DMF, CH_2Cl_2; (c) CH_2Cl_2, 13 kbar, 25 °C, 2 days; (d) DIBAL, toluene, −78 °C, 1 h; (e) imidazole, TIPSCl, DMF; (f) (i) *n*-BuLi, THF; (ii) Me_3SnCl, −30 °C, 1 h.



Scheme 49. Reagents and conditions: (a) 10 mol % $Pd(Ph_3)_4$, CuI, DMF, rt, 30 min; (b) xylenes, reflux, 2 h; (c) DDQ, 0 °C, 2 h; (d) MnO_2, CH_2Cl_2; (e) *n*-PrMgCl; (f) 10 mol % PTSA; (g) 2,6-lutidine, TMSOTf.

alcohol obtained. The ketone **220** underwent a Wittig olefination followed by metalation, leading to the stannane **221**. A Stille coupling of **221** with the triflate **203**, generated **207**, which could undergo electrocyclic cyclization after heating. An aromatization in oxidative conditions with MnO_2 formed the indoline **222**.

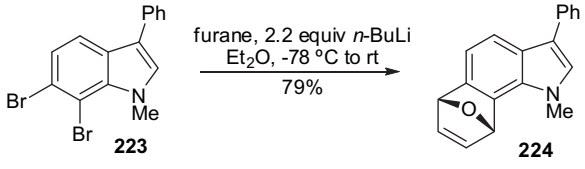
Deprotection of the nitrogen, followed by aromatization afforded (±)-*cis*-trikentrin A (Scheme 50). In summary, using a Stille coupling followed by an electrocyclic ring closure as key steps, Funk and Huntley accomplished a convergent total synthesis of (±)-*cis*-trikentrin A and of (±)-*cis*-trikentrin B.[17]



Scheme 50. Reagents and conditions: (a) EtLi, −78 °C; (b) 10 mol % TPAP, NMO; (c) Ph_3OMeBr, *n*-BuLi; (d) (i) *n*-BuLi, THF; (ii) Me_3SnCl, −30 °C, 1 h; (e) **203**, LiCl, 10 mol % $Pd(Ph_3)_4$, CuI, DMF, rt, 30 min; (f) toluene, 80 °C, 30 min; (g) MnO_2, CH_2Cl_2, 0 °C; (h) 2,6-lutidine, TMSOTf; (i) 10 mol % Co(salen), O_2, MeOH.

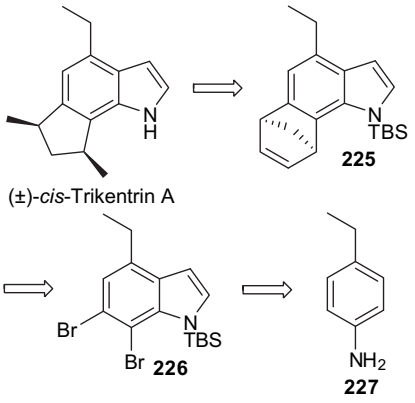
2.8. Syntheses of Buszek and co-workers

Buszek and co-workers studied the cycloaddition reaction between dibrominated indoles and furan in the presence of butyl lithium, as exemplified for the transformation of **223** into **224** (Scheme 51).[51] Presumably, this reaction occurs through an aryne intermediate. These results inspired the authors to use this reaction in the synthesis of (±)-*cis*-trikentrin A and of (±)-herbindole A.[19] The target molecules would be prepared by the oxidative cleavage of a tetracyclic intermediate (**225** and **228**). An analogous strategy has been used in other synthesis of trikentrins and herbindoles to obtain the required 1,3-*cis*-dimethylcyclopentane moiety (Schemes 20, 34, and 35). The required cyclic system of **225** and of **228** would be prepared from, respectively, the dibromo indoles **226** and **229**, using the methodology developed in the group. The indoles **226** and **229** would be synthesized from a functionalized benzene (**227** and **230**, respectively), using a Bartoli reaction to assemble the indole ring system (Schemes 52 and 53).

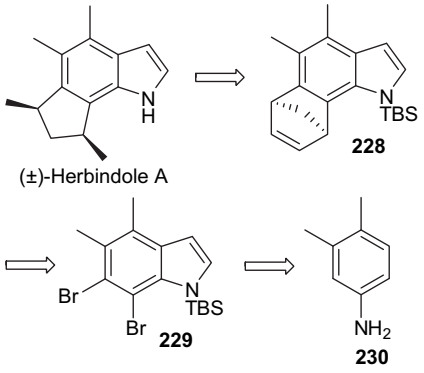


Scheme 51.

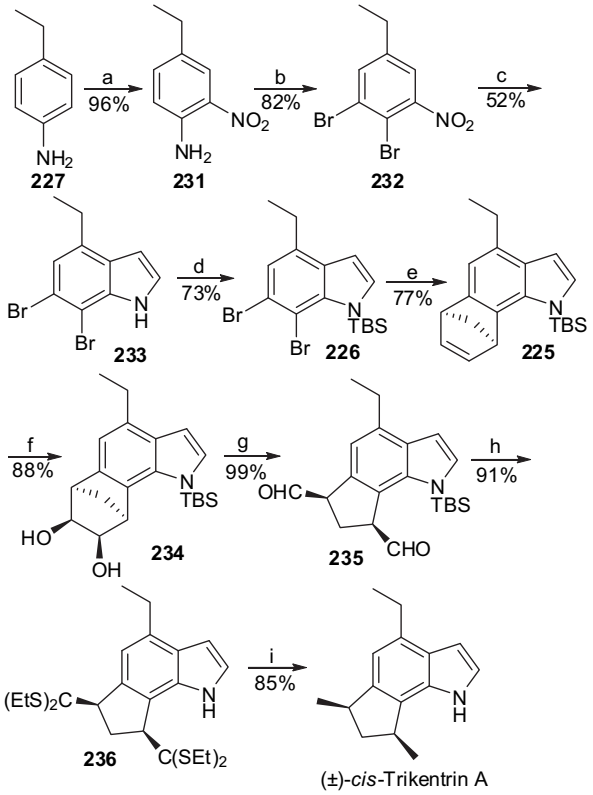
The synthesis of (±)-*cis*-trikentrin A began from ethylaniline (**227**), which underwent a nitration affording **231**. This compound was brominated and diazotized with *t*-BuONO, leading to **232**. The Bartoli reaction of **232** gave indole **233**. Protection of the indole with TBSOTf yielded **226**, which was submitted to a cycloaddition with pentadiene giving **225**. Dihydroxylation with OsO_4 of **225** and oxidative cleavage of the diol afforded the dialdehyde **235**. This compound was transformed into the corresponding thioketal **263**, which was reduced with Raney nickel leading to (±)-*cis*-trikentrin A (Scheme 54). The synthesis of (±)-herbindole A followed a similar reaction sequence, where the main difference is the starting material (Scheme 55). Thus, using an electrocyclic reaction as key step,



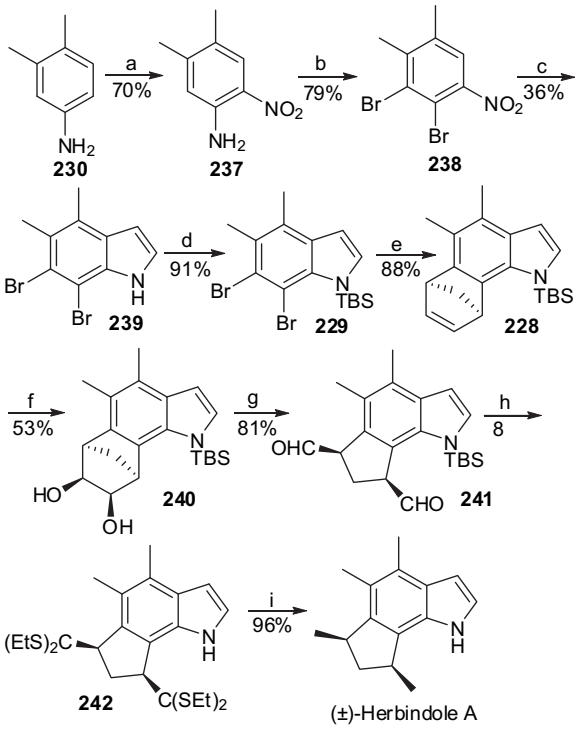
Scheme 52.



Scheme 53.



Scheme 54. Reagents and conditions: (a) (i) Ac_2O, CH_2Cl_2, 80 °C, 1 h, (ii) 50 °C, HNO_3, 1 h, (iii) NaOH, H_2O, $ClCH_2CH_2Cl$, 80 °C, 5 h; (b) (i) CuBr, Br_2, CH_3CN, 50 °C, 40 min, (ii) *t*-BuONO, CH_3CN, 50 °C, 30 min; (c) CH_2=CHMgBr, THF, −40 °C, 30 min; (d) KHMDS, TBSOTf, THF, −78 °C, 30 min; (e) (i) cyclopentadiene, toluene; (ii) −78 °C, *n*-BuLi, 30 min, H^+; (f) OsO_4, NMO, THF/H_2O, 6 h; (g) $NaIO_4$, THF/H_2O, rt, 1 h; (h) EtSH, $BF_3 \cdot Et_2O$, −78 °C to rt; (i) Raney nickel, EtOH, reflux, 20 min.



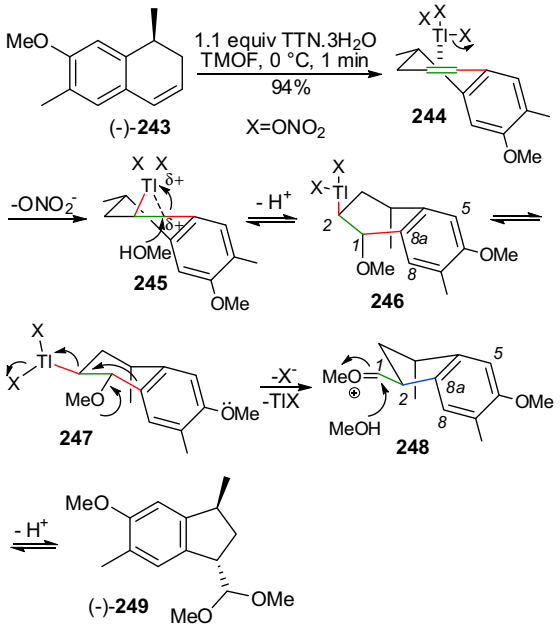
Scheme 55. Reagents and conditions: (a) (i) Ac_2O, CH_2Cl_2, 80 °C, 1 h, (ii) 50 °C, HNO_3, 1 h, (iii) NaOH, H_2O, $ClCH_2CH_2Cl$, 80 °C, 5 h; (b) (i) CuBr, Br_2, CH_3CN, 50 °C, 30 min, (ii) *t*-BuONO, CH_3CN, 50 °C, 30 min; (c) CH_2=CHMgBr, THF, −40 °C, 30 min; (d) KHMDS, TBSOTf, THF, −78 °C, 3 h; (e) (i) cyclopentadiene, toluene, (ii) −78 °C, *n*-BuLi, 30 min, H^+; (f) OsO_4, NMO, THF/H_2O, 2 h; (g) $NaIO_4$, THF/H_2O, rt, 2 h; (h) EtSH, $BF_3{\cdot}Et_2O$, −78 °C to rt; (i) Raney nickel, EtOH, reflux, 1.5 h.

(±)-*cis*-trikentrin A and (±)-herbindole A were synthesized by Buszek and co-workers.

2.9. Synthesis of Silva and co-workers

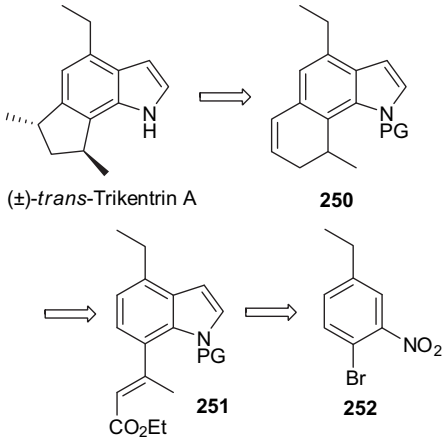
Ring contraction reactions are an important method to increase molecular complexity in a single step. Although new carbon–carbon bonds are not formed in these rearrangements, the reorganization of the bonds may occur with a high level of selectivity, affording products not easily accessible by other approaches.[52] Ring contraction reactions can be effected by acids, by bases, by oxidizers or photochemically.[52b] Among the oxidizers, one of the most used is thallium trinitrate (TTN).[52b,d] The ring contraction of 1-alkyl-1,2-dihydronaphthalenes mediated by thallium(III) or by iodine(III) is an efficient method to obtain *trans*-1,3-disubstituted indanes.[52,53] This reaction has been applied in the total synthesis of (+)-mutisianthol[54] and (±)-indatraline[55] The possible mechanism for the ring contraction of 1,2-dihydronaphthalenes explains the exclusive formation of the trans-diastereomer, as exemplified for alkene (−)-**243** using TTN in TMOF (trimethylorthoformate).[54,56,57] The reaction is initiated by coordination of thallium(III) to the double bond, leading to the cyclic thallonium ion **245**.[58–60] Nucleophilic attack of methanol (formed from hydrolysis of TMOF) at **245** occurs at the benzylic carbon atom giving the oxythallated adduct **246**, which equilibrates to the more stable conformer **247**. In this conformer the bonds are properly aligned for the rearrangement. Migration of the aryl group to carbon C2 with concomitant displacement of thallium(I) leads to the oxonium ion **248**. Finally, a second molecule of MeOH attacks **248** giving the ketal (−)-**249** (Scheme 56).

In 2008, our group described a diastereoselective synthesis of (±)-*trans*-trikentrin A. We envisioned that the target molecule could be obtained from a suitable tricyclic indole derivative, such as



Scheme 56.

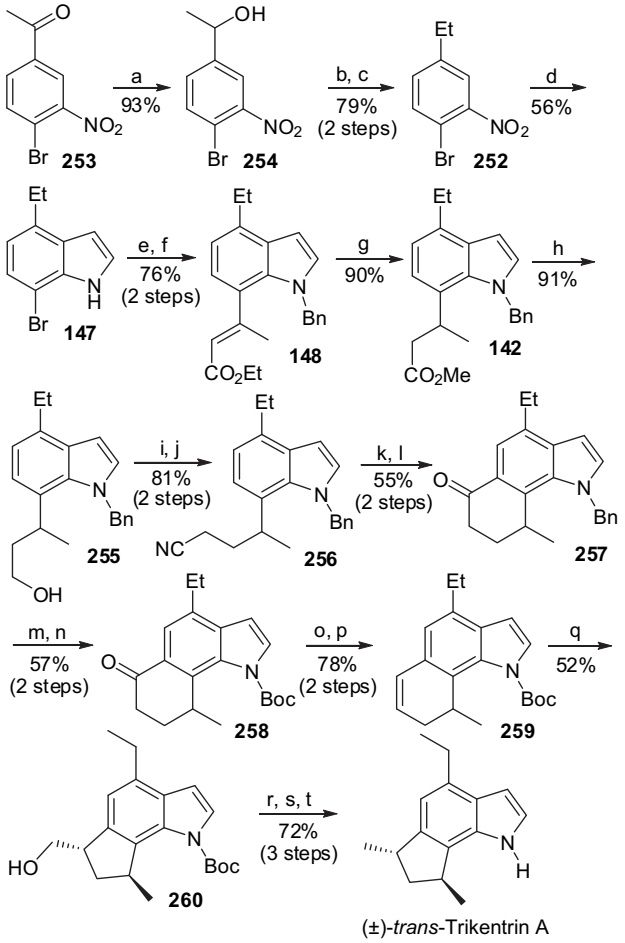
250, through a ring contraction reaction. The required indole **251** would be prepared from the functionalized benzene **252**. The nitro group would be used to construct the indole ring through Bartoli reaction. A Heck coupling would be performed on the bromine atom of **252** to install the unsaturated side chain of **251**, which would eventually originate a ring by a Friedel–Crafts acylation (Scheme 57).



Scheme 57.

The synthesis started transforming the commercially available acetophenone **253** into the functionalized benzene **252** in three steps. Bartoli reaction of the nitro compound **252** with vinylmagnesium bromide gave the indole **147**, which was protected with a benzyl group. Heck coupling with ethyl crotonate led to **148**. The double bond was reduced with magnesium in methanol and the ester group with DIBAL, delivering **255**, which was mesylated and treated with cyanide, yielding **256**. Hydrolysis of the nitrile gave a carboxylic acid, which was submitted to Friedel–Crafts acylation, giving the tricyclic ketone **257**. At this point, the protecting group of the indole was changed to Boc, because the ring contraction could not be performed in compound **250**, where PG is Bn. Thus, the benzyl group was removed treating **257** with anisole and $AlCl_3$ and the Boc group was inserted with Boc_2O, giving **258**. Reduction

followed by dehydration transformed the ketone into the corresponding olefin. The key ring contraction reaction was then performed treating **259** with thallium(III) nitrate (TTN) in acetonitrile. When TLC analysis indicated the formation of the ring contraction product, sodium borohydride was added to the mixture giving the alcohol **260** in a single operation. Only the trans-diastereomer is formed in this reaction. In addition, thallium(III) is chemoselective in this rearrangement reacting with the olefin, without oxidation of the indole moiety.[53b] To conclude the synthesis, the alcohol moiety of **260** was reduced to the corresponding alkane by tosylation followed by reaction with $LiAlH_4$. Deprotection of the indole ring with TBAF gave the desired alkaloid, as a single diastereomer. In summary, the synthesis of (±)-*trans*-trikentrin A was accomplished using as key reaction a chemo- and diastereoselective thallium(III)-promoted ring contraction reaction to construct the *trans*-1,3-disubstituted cyclopentyl unit (Scheme 58).



Scheme 58. Reagents and conditions: (a) 1.5 equiv $NaBH_4$, MeOH, 1 h; (b) 2 equiv Ph_3P, 2 equiv imidazole, 2 equiv I_2, 30 min; (c) 3 equiv $NaBH_4$, DMSO, 30 min; (d) 3.5 equiv CH_2=CHMgBr, THF, −45 °C, 45 min; (e) (i) 4.2 equiv KOH, DMSO, 1 h; (ii) 1.2 equiv BnBr, 1 h; (f) 16 equiv ethyl crotonate, 10 mol% $PdCl_2$, 20 mol% P(*o*-tolyl)$_3$, Et_3N, CH_3CN, 110 °C, 16 h; (g) MeOH, 10 equiv Mg, reflux, 18 h; (h) 4 equiv DIBAL, −40 °C, −20 °C, 40 min; (i) 2 equiv MsCl, Py (cat.), CH_2Cl_2, 12 h; (j) 2 equiv KCN, DMSO, 60 °C, 12 h; (k) 20% KOH, $HO(CH_2)_2OH$, 160 °C, 6 h; (l) TFA, TFAA, 0 °C, 3 min; (m) anisole, $AlCl_3$, 100 °C, 30 min; (n) 2 equiv Boc_2O, Py, DMAP, CH_3CN; (o) 3 equiv $NaBH_4$, MeOH, 0 °C, 1 h; (p) H_3PO_4, DMF, 80 °C, 2 h; (q) (i) 1.2 equiv TTN, CH_3CN, −40 °C, 3 min; (ii) 4.0 equiv $NaBH_4$, −40 °C to −20 °C; (r) 2 equiv TsCl, CH_2Cl_2; (s) 3 equiv $NaBH_4$, DMSO, 80 °C, 20 min; (t) 5 equiv TBAF, THF, reflux, 24 h.

3. Conclusions

The total syntheses of trikentrins and of herbindoles performed until 2009 are herein summarized. Nine research groups have been involved in the synthesis of these alkaloids and most of them accomplished the synthesis of more than one target molecule. Diels–Alder cycloaddition appears to be the most used reaction to form the skeleton of trikentrins and herbindoles. Kanematsu, Boger, and Kerr applied this reaction in their syntheses. Additionally, related pericyclic reactions are involved in the routes of Funk and of Buszek. The indole ring was constructed by three groups (Blechert, Buszek, and Silva) with the Bartoli reaction. Other important reactions for the synthesis of trikentrins and herbindoles are: radical cyclization (MacLeod), thermolysis of unsaturated azides (MacLeod), indolization of pyrroles (Natsume), intramolecular Heck reaction (Blechert), Stille coupling (Kerr), and ring contraction reaction (Silva). Finally, we hope this review will inspire new routes to these alkaloids, as well as to other molecules.

Acknowledgements

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Biographical sketch

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