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First total synthesis of the marine illudalane sesquiterpenoid alcyopterosin E

Bernhard Witulski,* Axel Zimmermann and Nicholas D. Gowans
Fachbereich Chemie, Universität Kaiserslautern, Erwin-Schrödinger-Strasse, D-67663 Kaiserslautern, Germany. E-mail: witulski@rhrk.uni-kl.de; Fax: +49 631 205 3921; Tel: +49 631 205 2032

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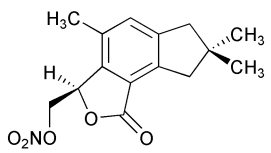
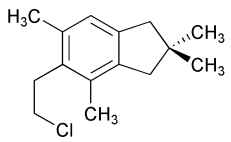
The first synthesis of the marine illudalane sesquiterpenoid alcyopterosin E was accomplished through a concise ABC ring-formation strategy using a rhodium(I)-catalysed intramolecular alkyne cyclotrimerisation as key connection.

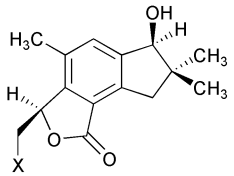
The alcyopterosins comprise a new set of the rare class of illudalane sesquiterpenoids whose isolation from the sub-Antarctic deep seawater soft coral *Alcyonium paessleri* was quite recently reported by Palermo *et al.*.[1] They represent the first ever illudalane sesquiterpenoids isolated from marine sources. Furthermore, alcyopterosin E (**1**) together with seven other alcyopterosins (B, C, F, G, H, J and M) are the first nitrate esters to be found in any natural product, while alcyopterosin A (**2**) and other examples of this series are chlorinated.[2] As judged by preliminary *in vitro* tests alcyopterosin E (**1**) showed mild cytotoxicity toward Hep-2 (human larynx carcinoma) cell line, while compound **2** was cytotoxic toward HT-29 (human colon carcinoma) cell line.[1] The unusual structures, the potential biological activities and the need to confirm the absolute stereochemistry of **1** as well as of other members of this family make them attractive synthetic targets.



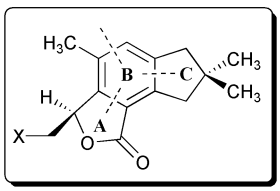
1: alcyopterosin E



2: alcyopterosin A



3: (X = ONO_2) **alcyopterosin M**
4: (X = Cl) **alcyopterosin L**



Herein we report the first total synthesis of naturally occurring (*R*)-alcyopterosin E (**1**) as well as the synthesis of its non-natural (*S*)-enantiomer. Our synthetic plan for the assembly of the tricyclic core of the alcyopterosins relies on a concise ABC ring-formation approach through a fully intramolecular rhodium(I)-catalysed alkyne cyclotrimerisation. Such a strategy not only secures a rapid and straightforward access to the tricyclic core of alcyopterosin E (**1**), moreover, the option that the underlying triyne itself can be assembled from two readily available building blocks through a simple esterification keeps the overall approach flexible enough to allow also future syntheses of other members of the alcyopterosin family or derivatives thereof.

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b2/b209573d/

Although several studies concerning the use of Wilkinson's catalyst [$RhCl(PPh_3)_3$] for alkyne cyclotrimerisations appeared in the recent literature,[3] applications of this catalytic three C–C bond forming process in the syntheses of natural products remained fairly rare.[4–7] In an elegant route to pterosin Z and calomelanolactone Stevenson used such an approach to gain the regiochemical control of the substitution pattern of these natural products.[4] At that time, tethered non-activated alkynes were subjected to rhodium(I)-catalysed intramolecular alkyne cyclotrimerisations. However, disconnection of the illudalane ring skeleton of alcyopterosin E (**1**) along an ABC ring-formation strategy leads to a triyne ester with an electron deficient alkyne unit and truly catalytic *intramolecular* alkyne cyclotrimerisations with electron deficient alkynes mediated by Wilkinson's catalyst have not been investigated so far.[8]

Our embarkment on the synthesis of alcyopterosin E (**1**) started with the syntheses of diyne acid **7** and propargylic alcohol (*R*)-**10** (Scheme 1).

Acid **7** was obtained from commercially available isophorone in six steps. Conversion of isophorone to ketone **5** was accomplished following literature proceedings by first epoxidation and then Eschenmoser α,β-epoxy ketone cleavage.[9] Silyl-protection of the terminal alkyne moiety in **5** with $ClSiMe_2Ph$ (98% yield) and subsequent conversion of the methyl ketone moiety into a terminal alkyne unit provided diyne **6** in 70% yield.[10] Thereafter carboxylation of **6** was reached by first deprotonation with *n*-butyllithium and second addition of gaseous carbon dioxide (89% yield). Once the acid functionality was introduced diyne acid **7** was obtained after removal of the silyl protective group with tetrabutylammonium fluoride (TBAF) in THF at 0 °C (94% yield).

Propargylic alcohol (*R*)-**10** was synthesised from (*S*)-glyceraldehyde acetonide (*S*)-**8** within four steps. (*S*)-glyceraldehyde acetonide is a widely used chiral building block for enantiomeric pure compounds and is easily available from L-ascorbic acid by a three step procedure.[11] An efficient transformation of (*S*)-**8** into diol (*R*)-**9** became possible applying a Corey–Fuchs reaction, followed by methylation of the *in situ* formed acetylide and subsequent cleavage of the acetonide protective group (37% yield over four steps). Finally, selective tosylation of the primary alcohol functionality in (*R*)-**9** gave propargylic alcohol (*R*)-**10** (69% yield). A tosyl group as protective group was chosen, because of its later use as a suitable leaving group for the implementation of the nitrate ester functionality.

With both building blocks—**7** and (*R*)-**10**—in hand their coupling to triyne ester (*R*)-**11** was investigated. Gratifyingly, a dicyclohexyl carbodiimide (DCC) mediated esterification proceeded uneventfully with retention of the absolute configuration. The reaction was carried out in the presence of catalytic amounts of dimethylamino pyridine (DMAP) in CH_2Cl_2 at −78 °C and was then brought to room temperature over a period of several hours. The thus formed enantiomerically pure triyne ester (*R*)-**11** was obtained in 70% yield after column chromatography on silica gel.

The assembly of the tricylic core of alcyopterosin E (**1**) along the projected ABC ring-formation strategy proceeded entirely efficiently by heating triyne ester (*R*)-**11** in the presence of 10

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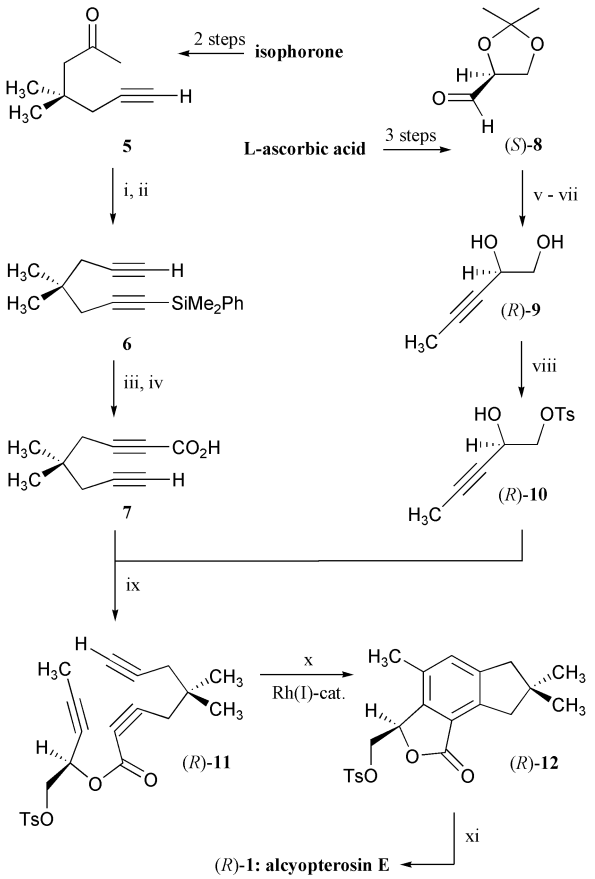

Scheme 1 *Reagents and conditions*: (i) LDA, THF, −78 °C, add $SiClMe_2Ph$, 98%; (ii) LDA, THF, −78 °C, add $POCl(OEt)_2$, then addition of LDA, −78 °C to r.t., 70%; (iii) *n*-BuLi, THF, −40 °C, add CO_2 (gas), 89%; (iv) TBAF, THF, 0 °C, 94%; (v) Zn, CBr_4, PPh_3, CH_2Cl_2, 61%; (vi) *n*-BuLi (2.2 equiv.), THF, −78 °C, then add MeI; (vii) *p*-TsOH, MeOH, 61% over two steps; (viii) *p*-TsCl, pyridine–CH_2Cl_2, 69%; (ix) DCC, DMAP, CH_2Cl_2, −78 °C to rt, 70%; (x) 10 mol% $[RhCl(PPh_3)_3]$, CH_2Cl_2, 40 °C, 72%; (xi) $NaNO_3$ (10 equiv.), Bu_4NNO_3, toluene, 110 °C, 69%.

mol% Wilkinson's catalyst.‡ Although smooth heating to 40 °C was required for completion of the reaction, high dilution conditions appeared to be unnecessary. Treatment of a 0.04 M solution of (*R*)-**11** (128 mg in 8 mL CH_2Cl_2) with 10 mol% $[RhCl(PPh_3)_3]$ gave (*R*)-**12** as a single product in 72% yield.

Finally, the first synthesis of alcyopterosin E (**1**) was completed by nucleophilic displacement of the tosyl protective group against a nitrate ester functionality. Such a nucleophilic substitution became feasible in toluene under phase transfer conditions using both an excess of sodium nitrate and tetrabutyl ammonium nitrate. Thus synthetic (*R*)-**1** was gained in 69% yield and showed NMR spectroscopic data which were superimposable on those of natural alcyopterosin E isolated from *Alcyonium paessleri*.§ The optical rotation of the synthetic (*R*)-configured material ($[\alpha]_D^{25}$ = −30.5 (*c* 2.35, $CHCl_3$)) was in agreement with that of the natural product ($[\alpha]_D^{25}$ = −31.28 (*c* 2.35, $CHCl_3$)[1] and thereby confirming its absolute configuration.

Notably, the reported strategy for the synthesis of (*R*)-alcyopterosin E (**1**) also allowed the synthesis of its non-natural (*S*)-enantiomer, because glyceraldehyde acetonide **8** is available in either enantiomeric form.[12] By starting from D-mannitol, the synthesis of (*R*)-**8**, (*S*)-**9**, (*S*)-**10** and finally the synthesis of the non-natural (*S*)-alcyopterosin E ($[\alpha]_D^{25}$ = +31.1 (*c* 2.35, $CHCl_3$)) was realised by applying the same synthesis sequence as outlined in Scheme 1 for (*R*)-**1**.

In conclusion, we have achieved an expedient, asymmetric synthesis of alcyopterosin E (**1**) from simple starting materials. The salient features of our synthesis includes a concise ABC ring-formation strategy to the tricyclic core of the targeted natural product by an intramolecular alkyne cyclotrimerisation applying Wilkinson's catalyst. Furthermore, the option that the underlying tethered triyne is accessible through a simple esterification keeps the overall approach very flexible and should allow syntheses of other members of the alcyopterosin family—studies that are currently under investigation.

Notes and references

‡ A solution of diyne ester (*R*)-**11** (128 mg, 0.32 mmol) in dry CH_2Cl_2 (8 mL) was purged with argon for 15 min. After addition of 10 mol% of $[RhCl(PPh_3)_3]$ (29 mg, 0.03 mmol) the solution was stirred at 40 °C for 24 h. The reaction was quenched by filtration through a plug of silica gel, that was thereafter rinsed twice with CH_2Cl_2 (15 mL). Column chromatography (silica gel, hexanes–diethyl ether = 7:3 (v/v)) afforded (*R*)-**12** (91 mg, 71%) as a solid. M.p. 80–82 °C; $[\alpha]_D^{22}$ −89.2 (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 3 H), 1.19 (s, 3 H), 2.31 (s, 3 H), 2.45 (s, 3 H), 2.74 (d, *J* = 3.6 Hz, 2H), 2.99 (br s, 2H), 4.25 (dd, *J* = 5.4 and 11.5 Hz, 1H), 4.57 (dd, *J* = 2.4 and 11.5 Hz, 1H), 5.56 (dd, *J* = 1.9 and 5.2 Hz, 1H), 7.22 (br s, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.71 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 21.6, 28.7, 40.9, 44.7, 47.0, 68.2, 78.1, 122.4, 127.9, 129.9, 130.2, 131.9, 132.3, 140.7, 141.3, 145.2, 147.3, 169.8; MS (EI, 70 eV); *m*/*z* (%): 400 (M^+, 14); Anal. Calc. for $C_{22}H_{24}O_5S$: C, 65.98; H, 6.04. Found: C, 66.10; H, 6.17%.

§ $NaNO_3$ (123 mg, 1.45 mmol) and tetrabutylammonium nitrate (228 mg, 0.75 mmol) were added to a solution of (*R*)-**12** (58 mg, 0.15 mmol) in toluene (5 mL). The reaction mixture was heated to 110 °C for 5 h. Filtration and subsequent flash chromatography gave (*R*)-(**1**) (31 mg, 69%) as a colourless oil. All spectroscopic data of synthetic (*R*)-**1** were identical to those of natural alcyopterosin E.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.19 (s, 3H), 2.40 (s, 3H), 2.75 (br s, 2H), 3.04 (br s, 2H), 4.57 (dd, *J* = 12.7 and 6.8 Hz, 1H), 5.06 (dd, *J* = 12.6 and 2.2 Hz, 1H), 5.66 (dd, *J* = 6.8 and 2.2 Hz, 1H), 7.27 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 28.7, 28.7, 41.0, 169.7, 147.6, 141.8, 140.5, 132.1, 130.2, 122.3, 76.9, 71.6, 47.0, 44.7.

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