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Stereoselective construction of the tetracyclic scalarane skeleton from carvone

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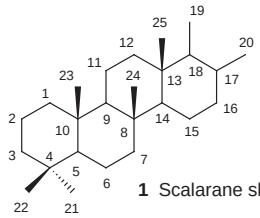
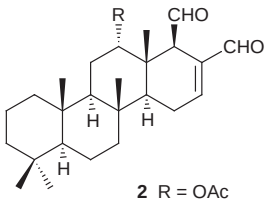
The tetracyclic scalarane skeleton 22 has been constructed from (*S*)-(+)-carvone using two intramolecular Diels–Alder reactions as key synthetic steps.

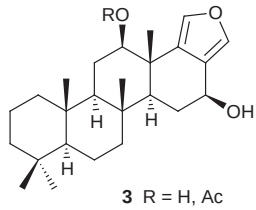
An increasing number of compounds of the relatively new family of the scalarane sesterterpenoids, which show structures based on the hypothetical scalarane skeleton **1**, have been isolated from different marine organisms.[1] These compounds



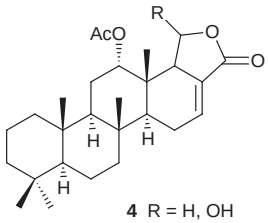
1 Scalarane skeleton



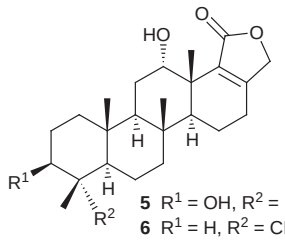
2 R = OAc



3 R = H, Ac



4 R = H, OH



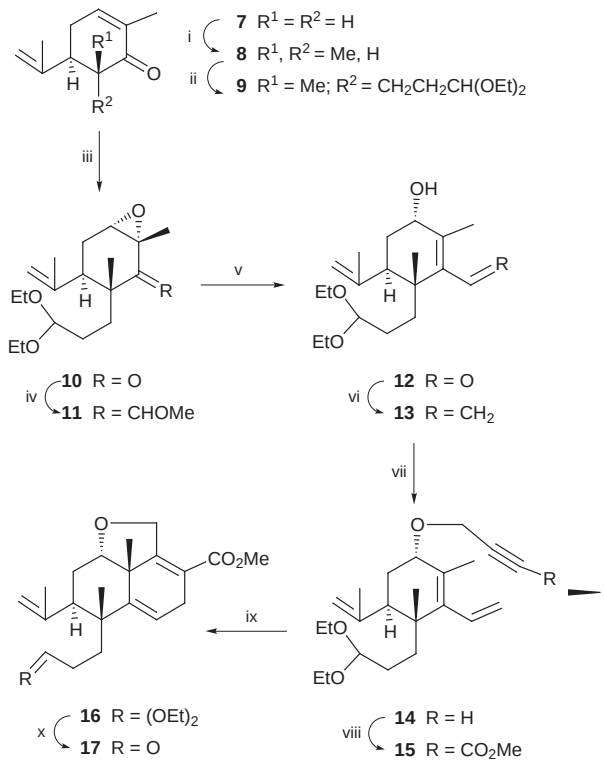
5 R^1 = OH, R^2 = Me
6 R^1 = H, R^2 = CH_2OH

seem to play an important ecological function[2] and some of them exhibit potentially useful biological activities, including antiinflammatory,[3] cytotoxic[4] and antifeedant[5] properties. Most of the members of this group of sesterterpenes possess a 1,4-dialdehyde moiety at C19–C20, either as actual aldehyde groups or latent as γ-butenolide or furan rings, as well as a C12 oxygenated function as common structural features. Recently some compounds with an additional oxygenated function at the C3 position have also been isolated.[6] Some representative compounds are scalaradial **2**, scalarafurans **3**, scalarolides **4**[4] and sesterstatins **5** and **6**.[7]

In spite of their interesting biological activities and challenging structures, this family of sesterterpenes has received little synthetic attention. To the best of our knowledge, only the synthesis of several compounds with the basic scalarane skeleton starting from manool,[8] methyl isocopalate[9] and methyl copalate,[10] as well as the total enantioselective biomimetic synthesis of scalarenedial[11] **2** (R = H) have been published. However, none of these syntheses solves the incorporation of the oxygenated function at the C12 position.

As part of our continuing interest in the synthesis of polycyclic natural products from readily available chiral building blocks,[12] we sought an efficient route to the scalarane sesterterpenes from carvone and we report herein a stereoselective general approach to the tetracyclic ABCD carbon framework. Explicitly, we describe the efficient preparation of the compound **22**, which has the scalarane skeleton and functionalisation suitable for further elaboration into some of the more representative natural scalaranes. The synthesis of **22** is effected using (*S*)-carvone as a C-ring synthon which is incorporated into the tetracyclic framework following a C→CD→ABCD ring annulation strategy, using two intramolecular Diels–Alder (IMDA) reactions as key synthetic steps.[13]

The synthesis commences with the preparation of the propargyl (prop-2-ynyl) compound **15**, precursor of the IMDA reaction that allows the construction of the CD ring subunit (Scheme 1). The known dialkylated carvone **9**, obtained in 70% overall yield from (*S*)-carvone by two consecutive alkylations with MeI and 3-iodopropanaldehyde diethyl acetal,[12a] was stereoselectively converted into the α-epoxy ketone **10** in 92% yield by treatment with alkaline H_2O_2. Treatment of **10** with the lithium derivative of methoxymethyl(diphenyl)phosphine oxide



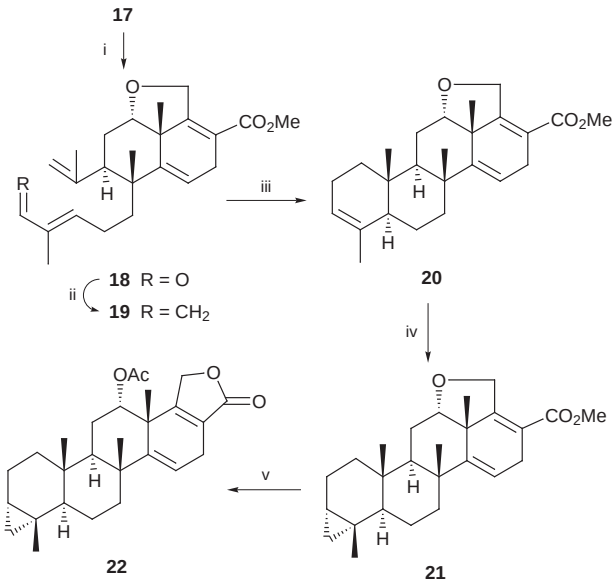
Scheme 1 *Reagents and conditions*: i, LDA, THF, −10 °C then CH_3I; ii, LDA, HMPA–THF, −78 °C then $(EtO)_2CHCH_2CH_2I$, 70% from **7**; iii, H_2O_2, NaOH, MeOH, room temp., 92%; iv, $Ph_2P(O)CH(Li)OMe$, THF, −78 °C then NaH, DMF, from 0 °C to room temp.; v, chromatography on silica gel, 77% from **10**; vi, $Ph_3P{=}CH_2$, THF, −20 °C, 85%; vii, Bu^n_4NI, $BrCH_2CCH$, 60% NaOH, room temp., 97%; viii, BuLi, THF, −78 °C then HMPA, $CNCO_2Me$, 87%; ix, toluene, 105 ºC, 99%; x, PPTS, acetone–H_2O, reflux, 87%.

in THF at low temperature afforded a mixture of crystalline β-hydroxyphosphine oxides, which were subjected to *syn* elimination by treatment with NaH in DMF at 0 °C to give a mixture of isomeric vinyl ethers **11**. Direct chromatographic purification of this mixture on silica gel resulted in chemoselective hydrolysis of the vinyl ether moiety and consecutive opening of the epoxide, providing the desired unsaturated hydroxy aldehyde **12** cleanly and efficiently (77% overall yield from epoxy ketone **10**).† Methylenation of **12** under Wittig conditions then gave dienol **13** in 85% yield, which was transformed into the propargyl ether **14** in very high yield by reaction with propargyl bromide under phase-transfer conditions. Sequential treatment of compound **14** with BuLi and methyl cyanoformate in the presence of added HMPA provided **15** in 87% yield, which underwent a smooth IMDA cycloaddition upon heating in a sealed tube at 105 °C overnight in anhydrous toluene. The reaction takes place very cleanly to give the tricyclic system **16** in nearly quantitative yield.[14]

After successfully accomplishing the synthesis of the CD ring fragment, attention was turned towards the construction of the AB rings, for which we followed a parallel route to that previously used by us for the preparation of a related system (Scheme 2).[12c] Removal of the aldehyde acetal function of **16** with PPTS in aqueous acetone afforded the aldehyde **17** in 87% yield. Wittig reaction of **17** with (α-formylethylidene)triphenylphosphorane provided the chain-extended aldehyde **18**, which by subsequent standard Wittig methylenation afforded the compound **19** in 78% overall yield. Heating a solution of this compound in toluene and a small amount of propylene oxide in a sealed tube at 185 ºC for 6 days afforded the pentacyclic compound **20**, with the expected *trans–anti–trans* fused ABC ring system of the scalarane framework, in 85% yield after column chromatography.

Completion of the synthesis of compound **22** was effected as follows. First **20** was submitted to Simmons-Smith cyclopropanation conditions to chemo- and stereoselectively cyclopropanate the ring A double bond, an indirect way of introducing the geminal dimethyl group at C-4 of the natural scalaranes. Finally, cleavage of the dihydrofuran ring of **21** occurred smoothly and cleanly by treatment with Ac_2O and zinc iodide, being accompanied by simultaneous lactonisation to give the scalarane-type compound **22**‡ in 86% overall yield for the last two steps.

The synthesis of **22** from (*S*)-(+)-carvone is thus completed in 15 synthetic operations in 17% overall yield. We believe that this compound constitutes an attractive intermediate for the synthesis of the more representative scalaranes. Work is currently in hand to further elaborate this intermediate towards scalaradial.§



Scheme 2 *Reagents and conditions*: i, Ph_3P=CMeCHO, benzene, reflux, 87%; ii, Ph_3P=CH_2, THF, −20 °C, 90%; iii, toluene, 185 °C, 85%; iv, Et_2Zn, CH_2I_2, toluene, room temp., 89%; v, ZnI_2, $(MeCO)_2O$, room temp., 96%.

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Notes and references

† Alternative procedures to effect the same transformation using different mild acidic conditions also promoted hydrolysis of the acetal moiety.

‡ All new compounds give satisfactory analytical and spectral data. *Selected data* for **16**: $[\alpha]_D^{21}$ −21.3 (*c* 2.8, $CHCl_3$); δ_H(300 MHz, $CDCl_3$) δ 5.75 (1H, dd, *J* 6.9, 1.8), 4.82 and 4.72 (1H each, each br s), 4.78 (1H, dd, *J* 15.5, 2.7), 4.58 (1H, dd, *J* 15.5, 3.8), 4.4 (1H, dd, *J* 5.3, 5.2), 4.17 (1H, dd, *J* 8.6, 4.5), 3.71 (3H, s), 3.61 and 3.44 (2H each, each m), 3.28 (1H, dd, *J* 20.7, 6.9), 2.73 (1H, m), (3H, s), 1.16 (6H, t, *J* 6.5), 1.11 (3H, s), 1.06 (3H, s). For **20**: $[\alpha]_D^{21}$ −44.7 (*c* 3.3, $CHCl_3$); mp 159–160 °C (from EtOH); δ_H(400 MHz, $CDCl_3$), 5.65 (1H, dd, *J* 6.5, 1.5), 5.27 (1H, br s), 4.96 (1H, dd, *J* 14, 2.4), 4.31 (1H, dd, *J* 14, 3.5), 3.92 (1H, dd, *J* 4.5, 1.7), 3.74 (3H, s), 3.34 (1H, dd, *J* 20.7, 6.5), 2.65 (1H, dddd, *J* 20.7, 3.5, 2.4, 1.5), 1.61 (3H, br s), 1.19 (3H, s), 1.107 (3H, s), 0.786 (3H, s). For **22**: $[\alpha]_D^{21}$ +82 (*c* 2.8, $CHCl_3$); mp 217–220 °C (from EtOH–acetone); δ_H(400 MHz, $CDCl_3$) 5.73 (1H, dd, *J* 4.6, 2.9), 4.93 (1H, dd, *J* 3.0, 2.2), 4.82 (1H, ddd, *J* 16.5, 3.3, 1.5), 4.48 (1H, ddd, *J* 16.5, 2.4, 2.3), 2.96 (1H, m), 2.82 (2H, m), 1.95 (3H, s), 1.42 (3H, s), 1.25 (3H, s), 0.98 (3H, s), 0.8 (1H, m), 0.82 (3H, s), 0.55 (1H, m), 0.44 (1H, dd, *J* 9.5, 4), 0.35 (1H, ddd, *J* 18.8, 12.7, 6.9), −0.03 (1H, dd, *J* 5.3, 4.0).

§ This transformation requires the establishment of a *trans* CD ring fusion. An initial experiment showed that the hydrogenation of the C14–C15 double bond of the alcohol resulting from hydrolysis of the acetate group of **22**, with $[Ir(cod)(py)(PCy_3)]PF_6$ takes place chemo- and stereo-selectively to give the required *trans* CD ring fusion.

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