The Total Synthesis of Racemic Isoacanthodoral

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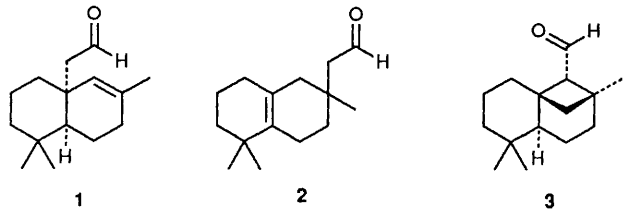
An efficient total synthesis of the marine sesquiterpenoid isoacanthodoral **1** has been achieved using an intermolecular Diels–Alder approach.

Isoacanthodoral **1** is a structurally unique sesquiterpenoid isolated from the dorid nudibranch *Acanthodoris nanaimoensis*, along with its congeners nanaimoal **2** and acanthodoral **3**, as a mixture.[1] This mixture, which was found to possess antibacterial, antifungal and antifeedant activities,[2] gave separable 2,4-dinitrophenylhydrazone (2,4-DNP) derivatives.[2] The structure of the 2,4-DNP derived from isoacanthodoral was determined by a single-crystal X-ray diffraction analysis.[1a] Herein, we describe an efficient synthesis which provides access to pure isoacanthodoral **1** in racemic form. The synthesis also serves as direct proof of its structural assignment.

Several years ago, it was observed in this laboratory that the boron trifluoride-catalysed Diels–Alder reaction of dienone ester **4** and isoprene gave rise, predominantly (65% improved yield), to the '*anti-para*' adduct **5**.[3] This unusual regioselectiv-



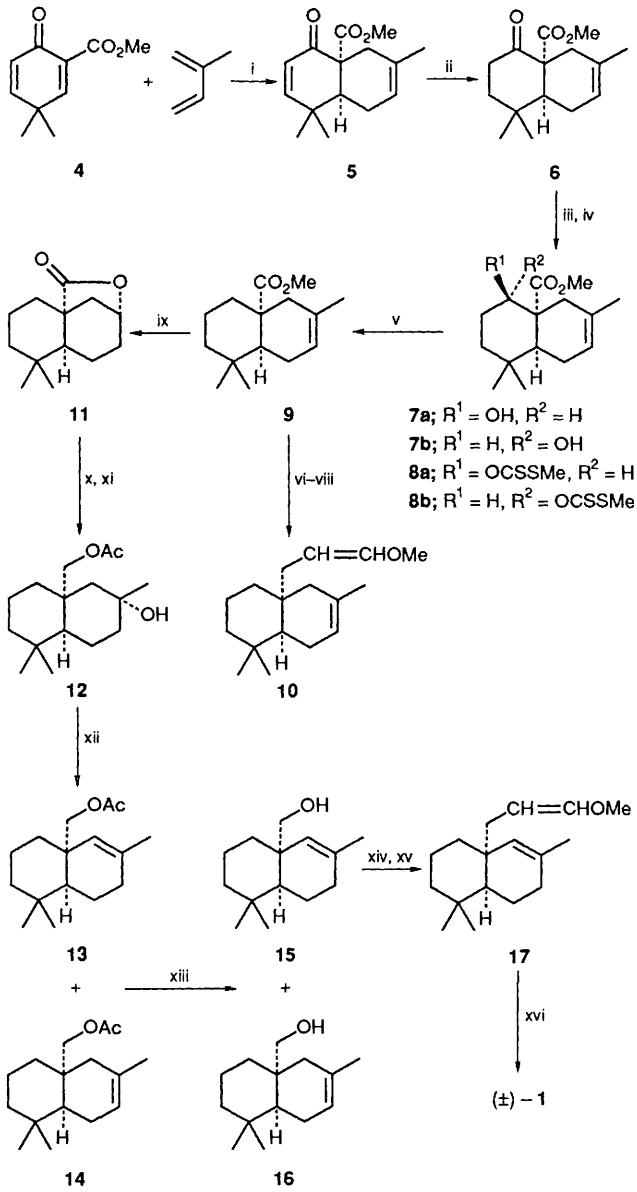
1 2 3

ity proved to be highly useful for the synthesis of the target molecule **1**, as it allows for a rapid assembly of the required carbon framework. Hydrosilylation of **5** with triethylsilane and Wilkinson's catalyst[4] gave the corresponding silyl enol ether, which was hydrolysed with aqueous potassium carbonate in methanol. When the saturated keto ester **6**, thus obtained in 97% yield, was treated with sodium borohydride in methanol at 0 °C, the desired hydroxy esters **7a** and **7b** (5 : 1) were formed along with a substantial amount of the over-reduced diols. The formation of these by-products could be suppressed by brief exposure (5 min) of **6** to the reducing agent at −40 °C. Under these conditions, a mixture of the epimeric alcohols **7a** and **7b** was formed in virtually quantitative yield.

The deoxygenation of the alcohols **7a–7b** was effected as follows. Treatment with sodium hydride, carbon disulphide and methyl iodide in 1,2-dimethoxyethane gave rise to the corresponding xanthates **8a** and **8b**. Subsequent reduction with tri-n-butyltin hydride in refluxing toluene in the presence of a catalytic amount of azoisobutyronitrile[5] (AIBN) gave ester **9** [IR (neat) 1730 cm^{-1} (ester); ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (br. s, 1H, –CH=), 3.68 (s, 3H, OMe), 1.64 (s, 3H, Me), 0.96 (s, 3H, Me) and 0.88 (s, 3H, Me); *m/z* M^+ 236.1780 (calc. for $C_{15}H_{24}O_2$: 236.1778)] in 90% yield over two steps.

The conversion of ester **9** to isoacanthodoral **1** requires two major operations: the migration of the double bond and a one-carbon extension of the angular substituent. Initial attempts were made to extend the carbon chain first. Towards this end, ester **9** was reduced with lithium aluminium hydride. Subsequent oxidation of the resulting alcohol with pyridinium chlorochromate (PCC) on alumina,[6] followed by a Wittig reaction with methoxymethylenetriphenylphosphorane[7] of the aldehyde thus formed, afforded the desired enol ethers **10**. Unfortunately, under no conditions applied could the enol ether moiety present in **10** be converted to the required aldehyde group. Invariably, a complex mixture was formed, presumably because of side reactions initiated by an intramolecular Prins-type process involving either the starting material or the expected product.

In an alternative approach which proved to be successful, ester **9** was first converted to lactone **11** [IR (CH_2Cl_2, cast) 1753 cm^{-1} (lactone); ^1H NMR (400 MHz, $CDCl_3$) δ 1.45, 1.01 and 0.95 (all s, 3H each, 3 × Me); *m/z* M^+ 222.1619 (calc. for $C_{14}H_{22}O_2$: 222.1620)] in quantitative yield by treatment with toluene-*p*-sulphonic acid in refluxing benzene. Lithium aluminium hydride reduction of **11** followed by selective acetylation (acetic anhydride in pyridine) of the resulting diol gave rise to hydroxy acetate **12** (90% yield). A large number of conditions were examined for the dehydration of **12**. The best results were obtained when the reaction was carried out at −40 °C with a large excess of phosphorus oxide trichloride in pyridine in the presence of 4-dimethylaminopyridine (DMAP). Under these conditions, the desired unsaturated compound **13** was produced predominantly, along with its regioisomer **14**, in a total yield of 95%. The ratio of these two isomers was determined to be 3 : 1 on the basis of the NMR spectrum (400 MHz, $CDCl_3$) which showed two broad singlets for the olefinic protons with the major at δ 5.15 and the minor at δ 5.28. These isomeric olefins were hydrolysed with



4 5 6 11 9 12 10 13 15 17 14 16

Reagents and conditions: i, $BF_3{\cdot}Et_2O$; ii, $(Ph_3P)_3RhCl$, Et_3SiH, then 10% aq. K_2CO_3, MeOH; iii, $NaBH_4$; iv, NaH, CS_2, MeI; v, Bu^n_3SnH, AIBN; vi, $LiAlH_4$; vii, PCC–Al_2O_3; viii, Ph_3P=CHOMe; ix, *p*-$MeC_6H_4SO_3H$; x, $LiAlH_4$; xi, Ac_2O-pyridine; xii, DMAP, $POCl_3$-pyridine; xiii, aq. K_2CO_3, MeOH; xiv, PCC-Al_2O_3; xv, Ph_3P=CHOMe; xvi, aq. ACOH, SiO_2

aqueous potassium carbonate in refluxing methanol and the resulting alcohols **15** and **16** (3 : 1 ratio, 90% yield) separated by flash chromatography on silica gel. Oxidation of the pure alcohol **15**, isolated in 44% yield, with pyridinium chlorochromate on alumina to the corresponding aldehyde, followed by treatment with methoxymethylenetriphenylphosphorane, resulted in the formation of enol ethers **17** (85% yield). When this isomeric mixture was exposed to silica gel containing a small amount of aqueous acetic acid, a 95% yield of (±)-isoacanthodoral **1** was isolated. The synthetic compound showed spectral data [IR ($CHCl_3$, cast) 2845, 2720 and 1720 cm^{-1} (CHO); ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (dd, 1H, *J* = *J'* = 3 Hz, CHO), 5.23 (d, 1H, *J* 1 Hz, –CH=), 2.71 (dd, 1H, *J* 15, *J'* 3 Hz, CH_2CHO), 2.13 (dd, 1H, *J* 15, *J'* 3 Hz, CH_2CHO), 2.0–1.7 (complex, 4H), 1.65 (s, 3H, Me), 1.5–1.1 (complex, 7H), 1.0 (s, 3H, Me) and 0.91 (s, 3H, Me); ^{13}C

NMR (100.6 MHz, $CDCl_3$) δ 204.8 (d), 135.5 (s), 129.9 (d), 57.2 (t), 46.3 (d), 40.1 (t), 38.5 (t), 38.2 (s), 34.2 (s), 32.4 (q), 28.9 (t), 26.4 (q), 23.5 (q), 19.9 (t) and 19.2 (t); *m/z* M^+ 220.1821 (calc. for $C_{15}H_{24}O$: 220.1827)] consistent with the structural assignment, and gave a 2,4-DNP derivative whose spectroscopic properties were found to be identical to those reported for the natural derivative.[1b]

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