Pergamon

Tetrahedron Letters, Vol. 35, No. 42, pp. 7841-7844, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01647-X

A Stereoselective Total Synthesis of Bakkenolide-A (Fukinanolide)

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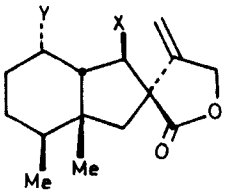
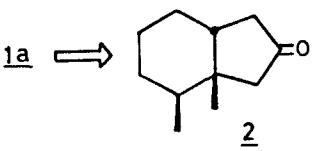
Abstract: *A highly stereoselective synthesis of bakkenolide-A (fukinanolide. 1a) employing the radical mediated spirannulation methodology is described.*

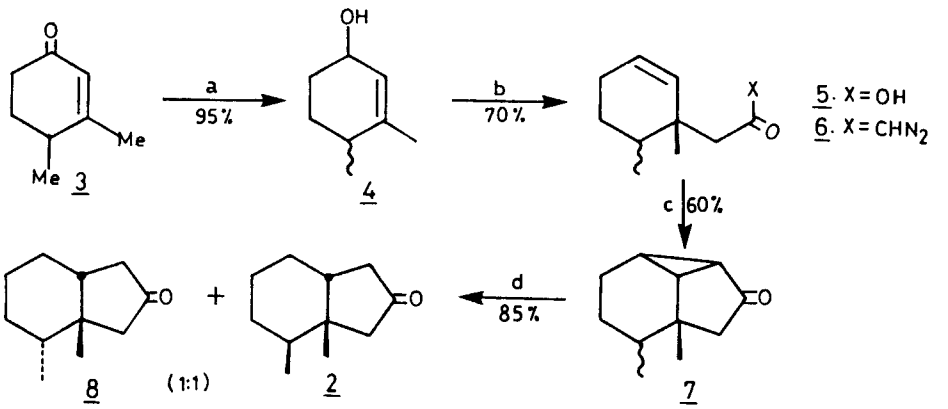
Bakkanes, biogenetically derived from eremophilanes, are an interesting class of sesquiterpenes containing an unique α-spiro-β-methylene-γ-butyrolactone fused to a hydrindane framework,[1] and have been shown to possess cytotoxic and antifeedant properties.[2] The simplest member of this class, Bakkenolide-A also known as Fukinanolide (1a), was first isolated[3] from the buds of the *Petasites japonicus* Subsp. *gigantus* Maxim. along with three other higher oxygenated analogues. Despite their established biological properties and novel structure, bakkanes have received only limited attention from synthetic chemists, and only two total synthetic approaches[4] to bakkenolide-A are reported in the literature. Herein we describe a highly stereoselective route to bakkenolide-A *via* radical mediated spirannulation of the hydrindanone 2.



1a. X=Y=H
1b. X=OAc, } Y=O-C(=O)-C(=CH2)-CH3
1c. X=OH, }
1d. X=OAc, Y=O-C(=O)-CH=C(SMe)-CH3

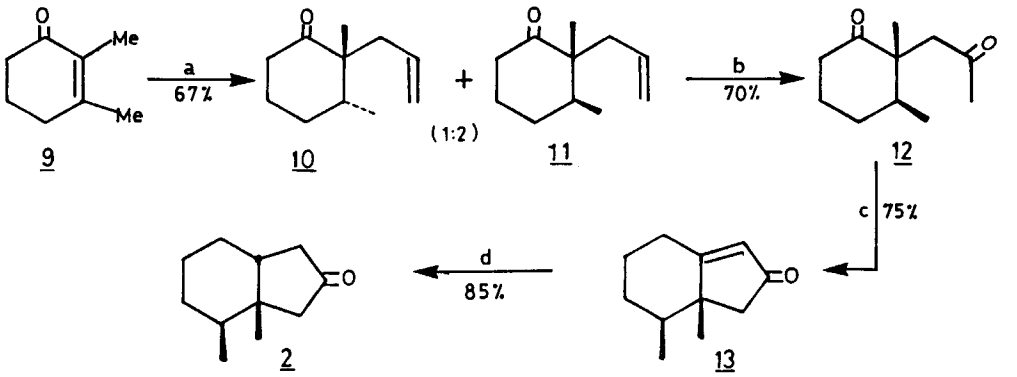


For the synthesis of the hydrindanone 2 first an intramolecular diazo ketone cyclopropanation strategy was adopted as depicted in the scheme 1. Thus, regiospecific $LiAlH_4$ reduction of 3,4-dimethylcyclohexenone (3) furnished a 2:1 epimeric mixture of the allyl alcohol 4 in 95% yield. The ortho ester Claisen rearrangement[5] with triethyl orthoacetate in the presence of a catalytic amount of propionic acid followed by hydrolysis of the



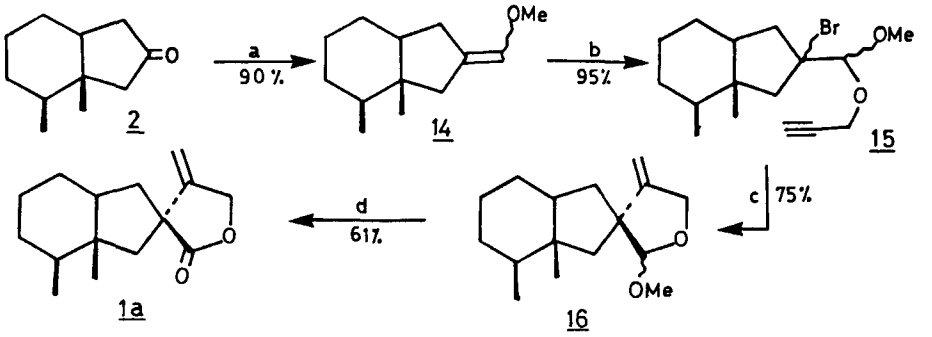
SCHEME 1: Reagents & Conditions: (a) $LiAlH_4$, Et_2O, -70°C, 2 hr; (b) (i) $MeC(OEt)_3$, EtCOOH, 180°C, 48 hr; (ii) 25% aq. NaOH, MeOH, reflux, 5 hr; (c) (i) $(COCl)_2$, C_6H_6, RT, 3 hr; (ii) CH_2N_2, Et_2O, 5 hr; (iii) An. $CuSO_4$, c-C_6H_{12}, W-lamp, reflux, 5 hr; (d) Li, liq. NH_3, 15 min.

resultant ester transformed the allyl alcohol 4 into the ene-acid 5 in 70% yield. Treatment of the acid chloride derived from the acid 5 with an excess of ethereal diazomethane generated the diazo ketone 6. Anhydrous copper sulfate catalysed decomposition[6] of the diazo ketone 6 in refluxing cyclohexane (tungsten lamp) followed by intramolecular insertion of the resultant keto-carbenoid in to olefin generated the cyclopropyl ketone 7 in 60% yield (from acid 5). Regiospecific reductive cleavage of the cyclopropane ring in 7 using lithium in liquid ammonia reduction conditions furnished a ≈1:1 mixture of the hydrindanones 2 and 8 in 85% yield, which can be separable by careful column chromatography on silica gel.[#] Since none of the intermediates 4-7 were found to be separable by conventional chromatography, an alternate route was developed for the hydrindanone 2, as

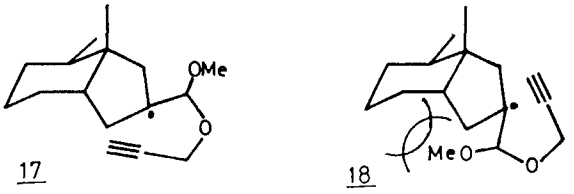


SCHEME 2: Reagents & Conditions: (a) (i) Li, liq. NH_3, THF, ^tBuOH, -33°C; (ii) CH_2=CH-CH_2Br, 5 hr; (10:11, 1:2); (b) $PdCl_2$, CuCl, O_2, DMF, H_2O, 5 hr; (c) 10%KOH, MeOH, 120°C, 3 hr; (d) H_2, 10% Pd/C, EtOAc, 4 hr.

depicted in the scheme 2. The requisite starting material 2,3-dimethylcyclohexenone (9) was obtained either by alkylation of the Hagemann's ester followed by decarboethoxylation[7] or by alkylation of 3-methylcyclohexenone with $K^+ {}^-O\text{-}{}^tBu$, ^tBuOH, MeI. Reductive alkylation reaction employing lithium-liquid ammonia-allyl bromide transformed the enone 9 into a 1:2 mixture of *cis*- and *trans*-allylated ketones 10 and 11[8] in 67% yield, which was separated by silica gel column chromatography. Oxidation of the allyl group in the major ketone 11 using Wacker conditions ($PdCl_2/CuCl/O_2/DMF\text{-}H_2O$)[8] furnished the 1,4-diketone 12 in 70% yield. Intramolecular aldol condensation (10% aq.KOH-MeOH) of the dione 12 followed by catalytic hydrogenation of the resultant cyclopentenone 13 furnished the hydrindanone 2[8] in 64% yield whose structure was confirmed by comparison of the ^1H NMR data with that reported in the literature.[4a] Radical cyclisation mediated spirannulation[9] transformed the hydrindanone 2 into bakkenolide-A (1a) with high degree of stereoselectivity as depicted in the scheme 3. Thus Wittig reaction of the hydrindanone 2 with methoxymethylenetriphenylphosphorane followed by treatment of the resultant enol ether 14 with N-bromosuccinimide (NBS) in the presence of propargyl alcohol generated the bromoacetal 15 in 85% yield. The 5-*exo*-*dig* radical cyclisation of the bromoacetal 15 using an *in situ* generated catalytic tri-n-butyltin hydride[10] in refluxing *t*-butanol ($^nBu_3SnCl/NaCNBH_3$) in the presence of a catalytic amount of azobisisobutyronitrile (AIBN) furnished the spiro hemiacetal 16, in 75% yield, with high degree of stereo- and regioselectivity. The high degree of stereoselectivity can be readily explained *via* the cyclisation of the less crowded *endo* radical 17 in preference to the *exo* radical 18. Finally hydrolysis of the hemiacetal



SCHEME 3: Reagents & Conditions: (a) $Ph_3P^+CH_2\text{-}OMe$, $K^+ {}^-O\text{-}{}^tamy$, THF, RT, 5 hr; (b) NBS, $HC{\equiv}CCH_2OH$, CH_2Cl_2, -70°C, 0.5 hr; (c) $^nBu_3SnCl$, $NaCNBH_3$, ^tBuOH, AIBN, reflux, 2 hr; (d) (i) 2.5 N HCl, THF, RT, 40 hr; (ii) PCC, CH_2Cl_2, RT, 3 hr.



followed by oxidation of the resultant lactol transformed hemiacetal 16 into bakkenolide-A (1a) in 61% yield, which exhibited the ^{1}H NMR signals [(270 MHz, $CDCl_3$) δ 5.07 and 4.99 ($C=CH_2$), 4.75 ($O-CH_2$), 0.97 (*tert*-Me), 0.82 (*sec*-Me, J=6.6 Hz)] identical with those of the authentic sample.

In conclusion, we have achieved a highly diastereoselective (in the ^{1}H NMR spectrum signals due to the spiro epimer were not present) total synthesis of bakkenolide-A. Currently we are investigating the extension of this methodology for the synthesis of chiral bakkenolide-A.

Acknowledgements: *We thank Prof. A.E. Greene for providing the ^{1}H NMR (200 MHz) spectrum of Bakkenolide-A. Financial assistance from the DST, New Delhi is gratefully acknowledged. TJR, SN and JAS thank UGC, CSIR and IISc respectively for the fellowships.*

#All the compounds exhibited satisfactory spectral data. Selected data for 11: IR (neat): 3078, 1702, 1638, 910 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 5.7 (1 H, m), 5.1 (1 H, m), 4.92 (1 H, m), 1.5-2.7 (9 H, m), 1.04 (3 H, s), 0.9 (3 H, d, J=7 Hz). For 2: IR (neat): 1740 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.4 and 1.9 (2 H, AB q, J=18 Hz), 2.22 (2 H, d, J=5 Hz), 1.15-1.65 (8 H, m), 1.04 (3 H, s), 0.8 (3 H, d, J=6 Hz). for 8: IR (neat): 1740 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.62 (1 H, dd, J=18.8, 7.2 Hz), 2.29 (1 H, d, J=18.4 Hz), 1.25-1.90 (10 H, m), 1.09 (3 H, s), 0.87 (3 H, d, J=6.6 Hz).

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(*Received in UK* 13 *July* 1994; *accepted* 26 *August* 1994)