Pergamon

Tetrahedron Letters, Vol. 35, No. 3, pp. 429-432, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(93)E0224-8

A Stereoselective Synthesis of (±)-Homogynolide-B

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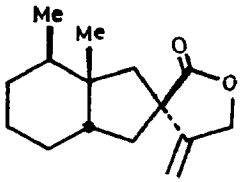
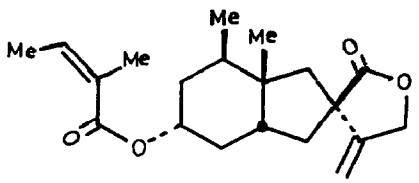
Abstract: *A highly stereoselective formal total synthesis of homogynolide-B via the ketoketals 4 and the ketospirolactone 3a starting from Hagemann's ester 2 is described.*

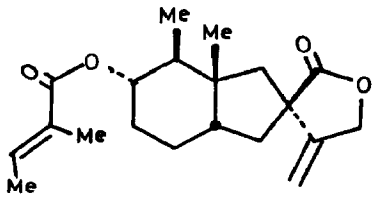
Bakkanes, are an interesting class of tricyclic sesquiterpenes embodying an unusual α-spiro-β-methylene-γ-butyrolactone fused to a hydrindane framework,[1] and have been shown to posses cytotoxic and antifeedant properties.[2] Homogynolide-B (**1**), a bakkane, was isolated from the neutral extracts of the plant *Homogyne alpina* (L.) Cass. along with bakkenolide-A and homogynolide-A.[3] Despite their established biological properties, bakkanes have received only limited attention from synthetic chemists,[4] and only one synthesis[5] of homogynolide-B has been reported so far. Herein we report a total synthesis of (±)-homogynolide-B starting from Hagemann's ester **2**.



Bakkenolide-A



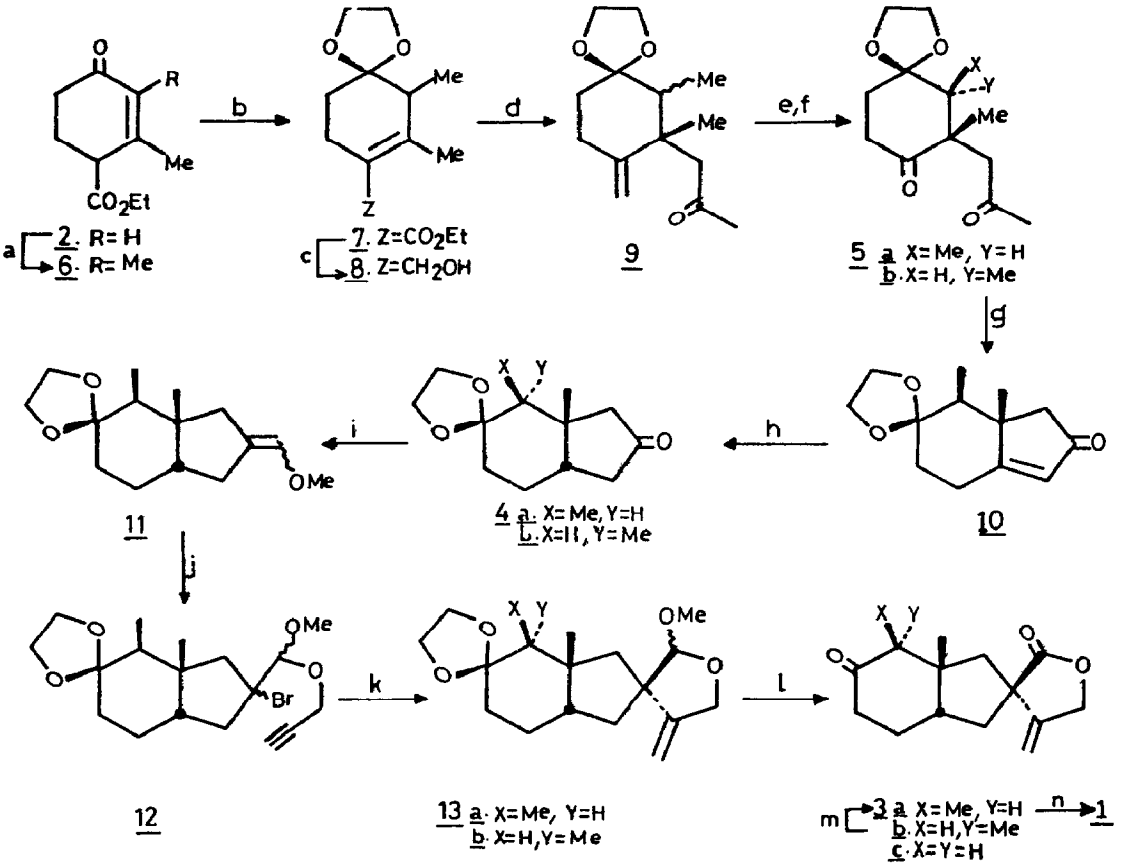
Homogynolide-A



Homogynolide-B (1)

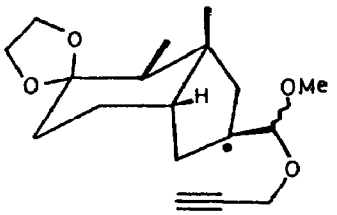
Retrosynthetic analysis of the homogynolide-B (**1**) readily identified the ketospirolactone **3a** and the ketoketal **4a** as the key intermediates. We therefore adopted the **2** → **5a** → **4a** → **3a** → **1** approach to homogynolide-B. As a model study first the sequence was carried out without the *sec.* methyl group, and Hagemann's ester **2** was successfully converted to the ketospirolactone **3c**. The same methodology has been extended for the synthesis of the ketospirolactone **3a** (Scheme 1). Thus, monomethylation of Hagemann's ester using sodium hydride and methyl iodide at −50°C cleanly furnished the γ-methylated product **6** in over 95% yield with only trace amounts of the α-alkylated product.[6] Ketalisation of **6** using the standard procedure

as reported[6] earlier gave the requisite olefin isomerised ketalester 7 in 50% yield along with the unisomerised ketalester (37%). Lithium aluminium hydride reduction of the ketalester 7 resulted in the allyl alcohol 8 in 97% yield in a regiospecific manner. The one pot Claisen rearrangement[7] of 8 with 2-methoxypropene in toluene in the presence of a catalytic amount of propionic acid furnished an inseparable epimeric mixture of the enone



***SCHEME 1*: Reagents and conditions**; (a) NaH, THF, MeI, −50°C, 5 h, 97%; (b) $(CH_2OH)_2$, p-TSA, C_6H_6, reflux, 40 h, 50%; (c) $LiAlH_4$, Et_2O, -70°C, 3 h, 97%; (d) CH_2=C(Me)—OMe, PhMe, sealed tube, 100°C, 10 h; 190°C, 48 h, 75%; (e) i. O_3/O_2, MeOH-CH_2Cl_2, −70°C; ii. Me_2S, −70°C → RT, 3 h, 80% (**5a**:**5b**, 3:2); (f) Chromatography on SiO_2; (g) KOH, MeOH, reflux, 4 h, 99%; (h) 10% Pd/C, H_2, EtOAc, 100%; (i) $Ph_3P^+CH_2OMe\ Cl^-$, $K^+\ ^-O^tAm$, THF, RT, 8 h, 75%; (j) NBS, HC≡C—CH_2OH, CH_2Cl_2, −50°C, 89%; (k) $^nBu_3SnCl$ (0.15 equi.), $NaCNBH_3$, AIBN (catalytic), ^{t}BuOH, reflux, 1.5 h, 76%; (l) i. 10% aq. HCl, THF, RT, 3 h, 80%; ii. PCC-silica gel, CH_2Cl_2, RT, 6 h, 93%; (m) DBU, CH_2Cl_2, RT, 3 h, 100%; (n) reference 5.

9. Ozonolysis of the epimeric mixture of **9** gave a 3:2 mixture of the epimeric diones **5a**,# mp. 90-92°C and **5b** in 75% yield, which was separated by silica gel chromatography. The generation of two epimers in the Claisen rearrangement is of no consequence since the wrong isomer can be isomerised to right one at a later stage (*vide infra*). However, the further sequence was carried out on individual isomers. The intramolecular aldol condensation of dione **5a** followed by the catalytic hydrogenation of the resultant cyclopentenone **10** furnished the ketoketal **4a**,# key intermediate in the sequence, in almost quantitative yield. A radical cyclisation methodology[8] was employed for the construction of the spirolactone moiety. Wittig reaction of **4a** with methoxymethylenetriphenylphosphorane resulted in the enol ether **11** in 75% yield, which on treatment with N-bromosuccinimide (NBS) in the presence of propargyl alcohol generated the bromoacetal **12** in 90% yield. The 5-*exo*-dig radical cyclisation of the bromoacetal **12** using an *in situ* generated[9] catalytic tri-n-butyltin hydride in refluxing *tert.* butanol ($^{n}Bu_3SnCl/NaCNBH_3$) in the presence of a catalytic amount of azoisobutyronitrile (AIBN) furnished the hemiacetal **13a** in 76% yield in a highly stereoselective manner. The preferential formation of **13a** can be rationalised via the cyclisation of the less crowded endo radical **14** resulting in the hemiacetal moiety to occupy exo orientation. Simultaneous hydrolysis of the ketal and hemiacetal moieties in **13a** with 10% aqueous HCl and THF followed by oxidation of the resultant ketolactol with PCC-silica gel furnished the ketospirolactone **3a**, mp. 100-101°C (lit.[5] 99-102°C), which exhibited IR and ^{1}H NMR spectra identical with those of the authentic sample.



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Same sequence of reactions as described above transformed the epimeric diketone **5b** into the hemiacetal **13b** via the ketoketal **4b**, mp. 78-81°C. Hydrolysis and PCC oxidation of the hemiacetal **13b** generated a 3:2 mixture of the ketospirolactones **3a** and **3b**, via the partial epimerisation of the methyl group during hydrolysis. Finally, equilibration of the epimeric mixture of **3a**:**3b** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) generated cleanly and quantitatively the ketospirolactone **3a**. Since Greene *et al.*,[5] have already converted the ketospirolactone **3a** into homogynolide-B via reduction followed by esterification, our synthesis of **3a** constitutes a formal total synthesis of (±)-homogynolide-B.

In conclusion, we have described here a highly stereoselective synthesis of homogynolide-B starting from Hagemanns' ester. Currently we are investigating the extension of this methodology for the synthesis of chiral homogynolide-B, which will be described in a full paper.

ACKNOWLEDGEMENTS: We thank Professor A.E. Greene for providing the copies of the IR and ^{1}H NMR spectra of the ketospirolactone **3a**. We are grateful to the DST, New Delhi for the financial assistance and SN thanks the CSIR, New Delhi for the award of a research fellowship.

All the compounds exhibited satisfactory spectral data (IR, ^{1}H and ^{13}C NMR and mass). Selected spectral data for the dione **5a**: IR (neat): ν_{max} 1705, 1070 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.9-4.15 (4 H, m, O–CH_2CH_2–O), 3.43 and 2.70 (2 H, AB q, J=17.4 Hz, CH_2Ac), 2.74 (1 H, d of t, J=13.2 and 5.5 Hz, H-6_{ax}), 2.40 (1 H, t of d, J=13.2 and 5.2 Hz, H-6_{eq}), 2.12 (1 H, t of d, J= 13.4 and 5.2 Hz, H-5_{eq}), 2.12 (3 H, s, $COCH_3$), 2.02 (1 H, q, J=7 Hz, CH–CH_3), 1.79 (1 H, d of t, J=13.3 and 5 Hz, H-5_{ax}), 1.17 (3 H, s, *tert.* CH_3), 0.95 (3 H, d, J=7 Hz, *sec.* CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 213.0 (s, C=O), 207.3 (s, C=O), 108.9 (s, O–C–O), 64.4 (t) and 65.5 (t) (O–CH_2CH_2–O), 49.7 (2 C, s and d), 47.6 (t, CH_2Ac), 35.6 (t, C–6), 35.4 (t, C–5), 31.3 (q, $COCH_3$), 21.2 (q, *tert.* CH_3), 9.0 (q, *sec.* CH_3). For the ketoketal **4a**: IR (neat): ν_{max} 1730, 1185, 1135 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.8-4.05 (4 H, m, O–CH_2CH_2–O), 2.83 and 1.91 (2 H, AB q, J=18.6 Hz, H–3), 2.61 (1 H, dd, J=18.8 and 7.4 Hz, H–1_{exo}), 1.3-2.0 (7 H, m), 1.1 (3 H, s, *tert.* CH_3), 0.905 (3 H, d, J=6.7 Hz, *sec.* CH_3). ^{13}C NMR (22.5 MHz, $CDCl_3$): δ 219.5 (s, C=O), 109.9 (s, O–C–O), 64.0 (t) and 66.0 (t) (O–CH_2CH_2–O), 45.4 (d), 44.2 (2 C, t), 43.6 (s, C–3a), 42.0 (d), 33.8 (t), 28.0 (2 C, t and q, C–7 and *tert.* CH_3), 8.6 (q, *sec.* CH_3).

References and notes

1. Fischer, N.H., Olivier, E.J. and Fischer, H.D. in *Progress in the Chemistry of Organic Natural Products*, Herz, H., Grisebach, H. and Kirby, G.W. Eds.; Springer-Verlag; New York 1979; Vol. 38, Chapter 2 and references cited therein.
2. Kano, K., Hayashi, K. and Mitsuhashi, H. *Chem. Pharm. Bull.*, **1982**, *30*, 1198 and references cited therein.
3. Harmatha, J., Samek, Z., Synackova, M., Novotny, L., Herout, V. and Sorm, F. *Collect. Czech. Chem. Commun.*, **1976**, *41*, 2047.
4. Bakkenolide-A: Evans, D.A., Sims, C.L. and Andrews, G.C. *J. Am. Chem. Soc.*, **1977**, *99*, 5453; Greene, A.E., Depres, J.-P, Coelho, F. and Brocksom, T.J. *J. Org. Chem.*, **1985**, *50*, 3943 and *Tetrahedron Lett.*, **1988**, *29*, 5661; Homogynolide-A: Hartmann, B., Kanazawa, A.M., Depres, J.-P. and Greene, A.E. *Tetrahedron Lett.*, **1991**, *32*, 767 and **1993**, *34*, 3875.
5. Coelho, F., Depres, J.-P., Brocksom, T.J. and Greene, A.E. *Tetrahedron Lett.*, **1989**, *30*, 565.
6. Other conditions are known to produce varying proportions of γ and α methylated products, *e.g.* NaOEt-MeI generates a 4:1 mixture, see White, J.D. and Sung, W.L. *J. Org. Chem.*, **1974**, *39*, 2323.
7. McKenzie, T.C. *Org. Prep. Proc. Int.*, **1987**, 435; Srikrishna, A. and Krishnan, K. *Indian J. Chem.*, **1990**, *29B*, 879 and references cited therein.
8. Srikrishna, A., Nagaraju, S. and Sharma, G.V.R. *J. Chem. Soc., Chem. Commun.*, 1993, 285 and references cited therein.
9. Stork, G. and Sher, P.M., *J. Am. Chem. Soc.*, **1986**, *108*, 303.

(*Received in UK* 4 *October* 1993; *accepted* 12 *November* 1993)