A Radical Cyclisation Strategy to α-Spiro-β-methylene-γ-butyrolactones. Total Synthesis of (±)-Norbakkenolide-A

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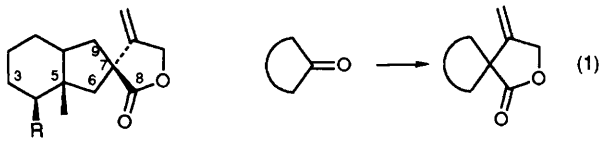
The 5-*exo-dig* radical cyclisation reaction of the bromoacetals **9**, obtained from the enol ethers **8**, and treatment of the resulting hemiacetal **10** with Jones' reagent transforms the cyclic ketones **7** and **12** into α-spiro-β-methylene-γ-butyrolactones **11** and norbakkenolide-A **2**.

Bakkenolide-A **1**, first isolated[1] from the bud of *Petasites japonicus* subsp. *giganteus Kitam*, is the simplest member of the bakkane class of sesquiterpenes containing a novel α-spirolactone fused hydrindane framework. Interestingly bakkenolide-A, which possesses an unconjugated β-methylene-γ-butyrolactone grouping, shows cytotoxic and antifeedant effects[2] normally associated with the conjugated α-methylene-γ-butyrolactones. In contrast to the many procedures that exist for obtaining α-methylene-γ-butyrolactones,[3] there are very few general methods available for the synthesis of

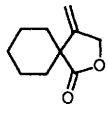
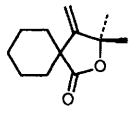
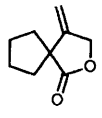
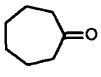
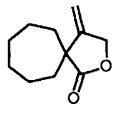
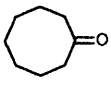
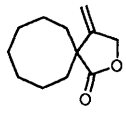
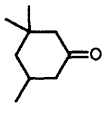
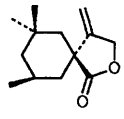
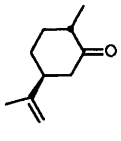
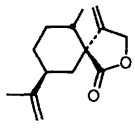
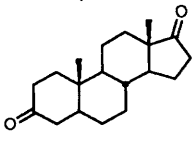
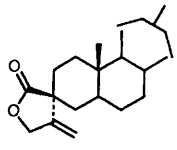
β-methylene-γ-butyrolactones.[4] The last decade has witnessed a rapid growth in the use of free radical cyclisation reactions in organic synthesis.[5] Stork and coworkers have developed a convenient method for the construction of butyrolactones *via* the 5-*exo-trig* radical cyclisation of mixed bromoacetals of allyl alcohols.[5] Herein we report a four step, efficient and general method for the transformation of cyclic ketones into α-spiro-β-methylene-γ-butyrolactones [eqn. (1)] employing a 5-*exo-dig* radical cyclisation reaction as the key step, and its extension to the total synthesis of (±)-norbakkenolide-A **2**.



1; R = Me
2; R = H

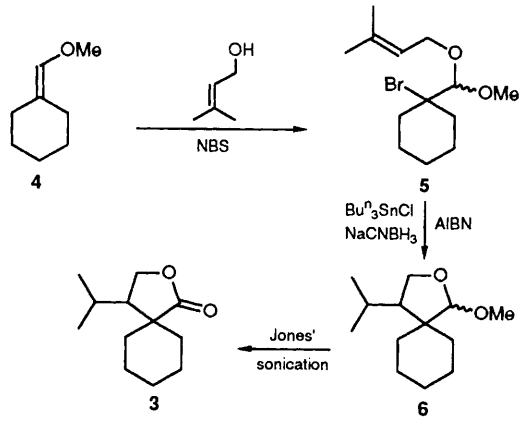
It was anticipated that the 5-*exo-trig* (or *dig*) radical cyclisation of a suitable cyclic tertiary bromide will generate the requisite spiro centre. It was first tested for the construction of α-spirobutyrolactone **3** as shown in Scheme 1. Thus, reaction of the enol ether **4**, readily available from cyclohexanone, with *N*-bromosuccinimide (NBS) in the presence of dimethylallyl alcohol furnished the mixed bromoacetal **5**. The 5-*exo-trig* radical cyclisation of the bromoacetal **5** using *in situ* generated catalytic Bu^n_3SnH (Bu^n_3SnCl, $NaCNBH_3$, Bu^tOH)[6] in the presence of a catalytic amount of azoisobutyronitrile (AIBN) furnished, regiospecifically, the spirohemiacetal **6**. The hemiacetal **6** was converted into the α-spirobutyrolactone **3** by sonochemically accelerated reaction with Jones' reagent.[7] The methodology has been extended to various β-methylene-α-spirobutyrolactones, as shown in Scheme 2. Thus, Wittig reaction on a cyclic ketone **7** with methoxymethylenetriphenylphosphorane followed by NBS bromination of the resultant enol ethers **8** in the presence of prop-2-ynyl alcohol (or dimethylprop-2-ynyl alcohol) generated the requisite radical precursors, acetylenic bromoacetals

Table 1 Synthesis of α-spiro-β-methylene-γ-butyrolactones[a]

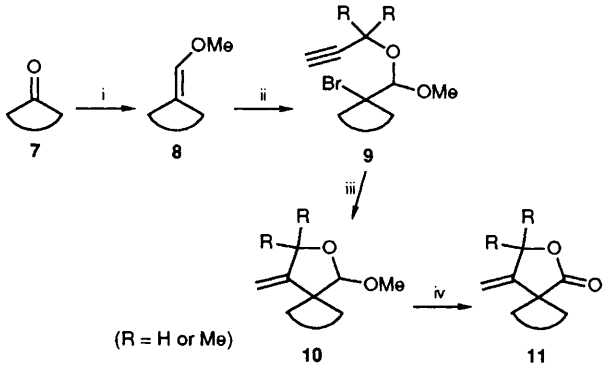
Entry	Ketone	Enol ether[b] (% yield)	Bromoacetal[b] **9** (% yield)	Spiroacetal[b] **10** (% yield)	Lactone (% yield)	
i		**4** (90)	**9a**† (92)	**10a**† (86)	**11a**† (96)	
ii	"		**9b** (52)	**10b** (70)	**11b** (63)	
iii		**8c** (80)	**9c** (90)	**10c** (82)	**11c** (79)	
iv		**8d** (90)	**9d** (97)	**10d** (91)	**11d** (92)	
v		**8e** (94)	**9e** (92)	**10e** (90)	**11e** (88)	
vi		**8f** (90)	**9f** (86)	**10f** (79)	**11f**[c] (90)	
vii		**8g** (83)	**9g** (59)	**10g** (70)	**11g**[c,d] (70)	
viii		**8h** (82)	**9h** (77)	**10h** (62)	**11h**[c,e] (78)	
ix	**12**	**8i** (96)	**9i** (93)	**10i** (90)	**2**† (94)[f]	

[a] All the compounds exhibited satisfactory spectral data. Yields refer to isolated and chromatographically pure products. [b] Mixture of stereoisomers. [c] Only one stereoisomer is formed. [d] $[\alpha]_D^{24}$ −41.3 (*c*, 0.75, $CHCl_3$). [e] M.p. 160–162 °C, $[\alpha]_D^{26}$ 63.6 (*c*, 1.4; $CHCl_3$). [f] 5 : 1 mixture of norbakkenolide **2** and its C-7 epimer.

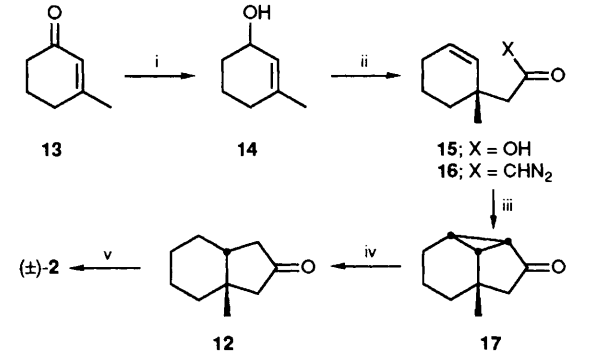
9. The 5-*exo*-*dig* radical cyclisation reaction of the bromoacetals **9** using *in situ* generated catalytic Bu^n_3SnH in the presence of AIBN followed by sonochemically accelerated reaction of the resultant spirohemiacetals **10** with Jones' reagent furnished α-spiro-β-methylene-γ-butyrolactones **11**. The results



Scheme 1



Scheme 2 *Reagents and conditions*: i, Ph_3P^+–CH_2OMe ^-Cl, $EtC(Me_2)O^-$ ^+K, tetrahydrofuran (THF)–$EtC(Me_2)$ OH, room temp., 2–5 h; ii, NBS, HC≡C–CR_2OH (R = H or Me), CH_2Cl_2, −40 °C, 0.5 h; iii, Bu^n_3SnCl (0.15 equiv.), $NaCNBH_3$ (2 equiv.), AIBN (catalytic), Bu^tOH, reflux, 1.5 h; iv, 1.6 mol dm^{-3} Jones' reagent, acetone, sonication, 5–15 min



Scheme 3 *Reagents and conditions*: i, $LiAlH_4$, Et_2O, −50 °C, 2 h, 95%; ii, (a) $MeC(OEt)_3$, $EtCO_2H$ (catalytic), 180 °C, 6 days; (b) 10% aq. NaOH–MeOH (1 : 1), reflux, 7 h, 60% from **14**; iii (a) C_6H_6, $(COCl)_2$, room temp., 1 h; (b) CH_2N_2, Et_2O, 2 h; (c) anhydrous $CuSO_4$, cyclohexane, reflux (W-lamp), 4 h, 48% from the acid **15**; iv, Li, liquid NH_3, 15 min, 80%; v, same as Scheme 2, for yields see Table 1

are summarised in Table 1. It is worth mentioning that in entries vi–viii, the radical cyclisation reaction proceeded with a high degree of stereoselectivity *via* the preferred less crowded axial radical, and yielded only one isomer of the butyrolactone after reaction with Jones' reagent.

For the synthesis of norbakkenolide **2**, the hydrindanone[8] **12** was identified as the requisite precursor, for which a new synthesis has been developed as depicted in Scheme 3. Regiospecific reduction of 3-methylcyclohexenone **13** with $LiAlH_4$ gave the allyl alcohol **14**. The ortho ester Claisen rearrangement[9] of the alcohol **14** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid, followed by hydrolysis of the resultant ester furnished the acid **15** in 60% yield. Treatment of the acid chloride derived from the acid **15**, with an excess of ethereal diazomethane generated the diazo ketone **16**. Anhydrous copper sulfate catalysed decomposition[10] of the diazo ketone **16** in refluxing cyclohexane (W-lamp) resulted in the cyclopropyl ketone **17** (48% from the acid **15**).† Regiospecific cleavage of the cyclopropane ring in **17** with lithium in liquid ammonia produced the hydrindanone[8] **12** in 80% yield. Finally, spirannulation as described above (Scheme 2), transformed the hydrindanone **12** into a 5 : 1 mixture of norbakkenolide **2**† and its C-7 epimer. The structure of the norbakkenolide was established based on the expected thermodynamically less crowded transition state in the radical cyclisation reaction, which was further confirmed by the NMR comparison with that of bakkenolide [two triplet (*J ca.* 2 Hz) signals due to olefinic protons appeared for **2** at δ 4.99 and 5.06; for the minor epimer at 5.05 and 5.2; whereas for bakkenolide[1] at 5.0 and 5.07].

In conclusion, an efficient method for transforming cyclic ketones into α-spiro-β-methylene-γ-butyrolactones using a radical cyclisation reaction as the key step, and its extension to the synthesis of (±)-norbakkenolide have been achieved. Since the 3-methylcyclohexenone can be enantioselectively reduced[11] to the 3-methylcyclohexenol by $LiAlH_4$ in the presence of chiral *N*-methylephedrine, the present route provides a convenient route to chiral norbakkenolide as well.

We thank Professor A. E. Greene for providing the ^1H NMR (200 MHz) spectrum of bakkenolide. S. N. and

† *Spectral data* for bromoacetal **9a**: ν_{max}/cm^{-1} (neat) 3290, 2120, 1449, 1194, 1122. δ_H (200 MHz, $CDCl_3$) 4.54 (1H, s, O–CH–O), 4.43 (2H, d, *J* 2.4 Hz, O–CH_2), 3.66 (3H, s, OMe), 2.49 (1H, t, *J* 2.4 Hz, C≡CH), 1.5–2.2 (10H, m). δ_C (22.5 MHz, $CDCl_3$) 107.8 (d, O–CH–O), 78.9 (s, *C*≡CH), 75.6 (s, C–Br), 75.0 (C≡CH), 58.9 (q, OMe), 56.1 (t, O–CH_2), 34.4 (t), 34.0 (t), 25.2 (t), 21.8 (2C, t). For hemiacetal **10a**: ν_{max}/cm^{-1} (CCl_4) 3076, 1182, 1095, 1023, 945, 933, 882. δ_H (200 MHz, $CDCl_3$) 4.88 (3H, m, O–CH–O and =CH_2), 4.49 and 4.39 (2H, t of AB q, *J* 13 and 2 Hz, 0–CH_2), 3.38 (3H, s, OMe), 0.8–2.0 (10H, m), δ_C (67.5 MHz, $CDCl_3$) 156.0 (*C*=CH_2), 108.8 (C=*C*H_2), 102.8 (O–CH–O), 69.9 (O–CH_2), 55.5 (OMe), 50.9 (spiro C), 37.1, 30.0, 26.5, 24.3 (2C). For lactone **11a**: ν_{max}/cm^{-1} (neat) 1776, 1671, 1452, 1353, 1170, 1113, 1029, 900. δ_H (200 MHz, $CDCl_3$) 5.17 (1H, t, *J* 2.1 Hz) and 5.08 (1H, t, *J* 2 Hz) (C=CH_2), 4.76 (2H, t, *J* 2 Hz, O–CH_2), 1.35–2.0 (10H, m). δ_C (22.5 MHz, $CDCl_3$) 179.7 (s, O=C–O), 149.1 (s, *C*=CH_2), 107.1 (t, C=*C*H_2), 69.1 (t, O–CH_2), 44.6 (s, spiro C), 33.2 (2C, t), 25.0 (t), 20.9 (2C, t). For cyclopropyl ketone **17**: ν_{max}/cm^{-1} (neat) 1722. δ_H (90 MHz, $CDCl_3$) 2.3 and 2.0 (2H, AB q, *J* 16 Hz, O=CCH_2), 1.0–2.1 (9H, m), 1.37 (3H, s, Me). δ_C (100 MHz, $CDCl_3$) 214.9 (s, C=O), 56.4 (t, O=*C*CH_2), 35.4 (d), 35.3 (d), 32.7 (d), 32.4 (s, *C*–Me), 30.3 (q, Me), 24.3 (d), 20.3 (t), 18.1 (t). For **2**: ν_{max}/cm^{-1} (neat) 1776, 1674, 1467, 1449, 1350, 1233, 1146, 1128, 1113, 1026, 894. δ_H (400 MHz, $CDCl_3$) 5.06 (1H, t, *J* 2.1 Hz) and 4.99 (1H, t, *J* 1.6 Hz) (C=CH_2), 4.78 (2H, t of AB q, *J ca.* 14 and 2 Hz, O–CH_2), 2.4 (1H, t, *J* 12.6 Hz, H-9a), 2.13 and 1.67 (2H, AB q, *J* 13.7 Hz, H-6), 1.9 (1H, m, H-10), 1.72 (1H, dd, *J* 12.7 and 6.2 Hz, H-9b), 1.2–1.7 (8H, m), 1.11 (3H, s, Me). δ_C (50 MHz, $CDCl_3$) 182.0 (O=*C*–O), 151.6 (*C*=CH_2), 105.4 (C=*C*H_2), 69.9 (OCH_2), 52.6 (C-6), 49.7 (spiro C), 44.7 (C-10), 41.7 (C-9), 40.7 (C-5), 33.0 (C-4), 24.9 (Me), 23.5, 22.3, 20.3. MS: *m/z* 220 (M^+, 75%), 133 (30), 111 (64), 110 (100), 95 (45), 81 (45).

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