Highly Stereoselective First Synthesis of an A-Ring-Functionalized Bakkane: Novel Free-Radical Approach to 9-Acetoxyfukinanolide

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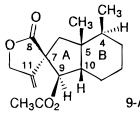
The bakkanes, novel spiro γ-butyrolactone hydrindane sesquiterpenes, include a small but growing number of terrestrial and marine natural products. Members of this class, with the exceptions of the archetype bakkenolide A and the octocoral-derived β,γ-epoxy lactone palmosalide C, are characterized by an acyloxyl function in the A and/or B rings and a methylene group at C-11.[1]

The unusual structural features of the bakkanes coupled with their associated biological effects[2] have produced in several laboratories efforts directed toward their preparation, which have culminated in the syntheses of (±)- and (+)-bakkenolide A,[3] (±)- and (−)-homogynolide A,[4] (±)-homogynolide B,[5] and (±)-palmosalide C.[6] However, since the vast majority of the bakkanes have, in addition to the spiro β-methylene-γ-butyrolactone moiety, an A-ring acyloxyl (generally acetoxyl) function at C-9, it is significant that the introduction of this latter feature has not been described to date. In this paper we report the synthesis of 9-acetoxyfukinanolide, one of several bakkanes isolated from the wild butterburs indigenous to Japan, *Petasites japonicus* maxim.[1g]

The highly stereoselective, efficient, and potentially general approach relies on a new free radical strategy for the introduction of the spiro β-methylene-γ-butyrolactone unit and a serendipidously discovered, thermodynamically driven retroaldol−aldol reaction for adjusting the stereochemistry at the vicinal C-7, C-9 stereocenters.



(-)-1
9-Acetoxyfukinanolide

The previously prepared[3c] dichloroketene−1,6-dimethylcyclohexene cycloadduct **3a** cleanly afforded in 63% yield from **2** cyclobutanone **3b**[7] on treatment with Zn in warm acetic acid (Scheme 1). Ring expansion of **3b** through exposure to ethyl diazoacetate in the presence of antimony pentachloride[8] was regioselective (81:19) in the desired sense and produced carbethoxycyclopentanone **4a** in 64% yield after purification on silica gel. Following conversion of **4a** to the corresponding propargyl ester **4b** by acid-catalyzed transesterification with propargyl alcohol in refluxing benzene, a novel free radical β-methylene-γ-butyrolactonization method was examined. To our delight, on exposure to ca. 2.5 equiv of manganese(III) acetate[9] in deoxygenated ethanol at 20 °C, keto ester **4b** underwent clean, selective 5-*exo dig* cyclization to provide a unique lactone (**5**), albeit of uncertain C-7 stereochemistry,[10] in 61% yield from **4a**.

Steric hindrance at the C-9 carbonyl in this product, as expected, rendered potentially selective hydride reducing agents

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(7) Yields are for purified, chromatographically homogeneous substances. Cyclobutanone **3b**: IR 1775, 1460 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.00−2.90 (m, 1 H), 2.74 (dd, J = 1.0, 15.4 Hz, 1 H), 2.53 (dd, J = 1.7, 15.4 Hz, 1 H), 1.85−2.00 (m, 1 H), 1.70−0.90 (m, 6 H), 1.26 (s, 3 H), 0.93 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (20.1 MHz, $CDCl_3$) δ 208.3 (C), 64.5 (CH_2), 57.7 (CH), 38.7 (CH_2), 31.8 (C), 28.6 (CH or CH_3), 23.6 (CH or CH_3), 20.2 (CH or CH_3), 16.5 (CH_2); MS (EI) *m/z* 152 (M, 1.4), 67 (100). Keto ester **4a**: IR 1755, 1726 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.19 (q, J = 7.1 Hz, 2 H), 3.26 (dd, J = 8.9, 11.0 Hz, 1 H), 2.35 (dd, J = 8.9, 13.2 Hz, 1 H), 2.15−2.05 (m, 2 H), 1.87 (dd, J = 11.0, 13.2 Hz, 1 H), 1.70−0.90 (m, 6 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.11 (s, 3 H), 0.87 (d, J = 5.5 Hz, 3 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 211.3 (C), 169.6 (C), 61.0 (CH_2), 57.6 (CH), 51.9 (CH), 39.6 (C), 35.6 (CH_2), 34.7 (CH_3 or CH), 29.4 (CH_2), 22.6 (CH_2), 20.2 (CH_2), 19.3 (CH_3 or CH), 16.1 (CH_3 or CH), 13.8 (CH_3 or CH); MS (EI) *m/z* 238 (M^+, 25), 55 (100). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 70.11; H, 9.21. Ketone **5**: IR 3090, 1779, 1736, 1669 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.18−4.96 (m, 3 H), 4.82 (A of ABXX′, d of ps t, J =1.6, 12.8 Hz, 1 H), 2.63 (d, J = 14.4 Hz, 1 H), 2.42 (m, 1 H), 2.06−1.90 (m, 1 H), 1.71 (d, J = 14.4 Hz, 1 H), 1.70−0.80 (m, 6 H), 1.16 (s, 3 H), 0.93 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 207.8 (C), 174.9 (C), 145.2 (C), 106.8 (CH_2), 70.4 (CH_2), 61.0 (C), 54.5 (CH), 40.3 (CH_2), 38.5 (C), 35.1 (CH), 29.4 (CH_2), 21.8 (CH_2), 19.6 (CH_2), 19.3 (CH_3), 16.0 (CH_3); MS (EI) *m/z* 248 (M^+, 27), 41 (100). Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.64; H, 8.23. Hydroxy lactone **6**: mp 112−113 °C (dichloromethane−hexane); IR 3420, 3090, 1758, 1672 cm^{-1}; ^{1} H NMR (200 MHz, $CDCl_3$) δ 5.30 (br s, 1 H), 5.13 (ps t, 1 H), 4.87 (d of ps t, J = 2.7, 12.7 Hz, 1 H), 4.74 (d of ps t, J = 1.9, 12.7 Hz, 1 H), 4.51 (ps t, J = 10.5 Hz, 1 H), 2.39 (d, J = 14.5 Hz, 1 H), 1.82 (d, J = 10 Hz, OH), 1.58 (d, J = 14.5 Hz, 1 H), 1.90−1.40 (m, 8 H), 0.99 (s, 3 H), 0.84 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 182.8 (C), 147.9 (C), 108.9 (CH_2), 80.4 (CH), 72.0 (CH_2), 55.9 (C), 51.8 (CH), 46.9 (CH_2), 38.6 (C), 36.0 (CH), 30.7 (CH_2), 21.2 (CH_2), 20.9 (CH_2), 20.1 (CH_3), 16.5 (CH_3); MS (CI) *m/z* 268 (M^+ + 18, 100). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.09; H, 9.09. (±)-9-Acetoxyfukinanolide: mp 109.5−110.5 °C (dichloromethane−hexane); IR 3090, 1773, 1736, 1670, 1240 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.46 (d, J = 11.7 Hz, 1 H), 5.20 (m, 1 H), 5.14 (m, 1 H), 4.70 (ps t, J = 2.2 Hz, 2 H), 2.35 (m, 1 H), 2.19 (d, J = 14.4 Hz, 1 H), 2.07 (s, 3 H), 1.96 (d, J = 14.4 Hz, 1 H), 1.60−1.10 (m, 7 H), 1.04 (s, 3 H), 0.89 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 178.2 (C), 170.4 (C), 148.1 (C), 107.7 (CH_2), 82.9 (CH), 70.5 (CH_2), 54.1 (C), 49.5 (CH), 46.9 (CH_2), 40.0 (C), 36.1 (CH), 30.6 (CH_2), 21.0 (CH_2), 20.8 (CH_2), 19.4 (CH_3), 16.2 (CH_3); MS (EI) *m/z* 292 (M^+, 2), 43 (100). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.80; H, 8.11.

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(9) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363 and references cited therein. For related, but less efficient, recent protocols for effecting free-radical spiro lactonization, see: ref 4d. Back, G. B.; Gladstone, P. L.; Parvez, M. *J. Org. Chem.* **1996**, *61*, 3806−3814. Also see: Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y.-J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Keller, D.; Kleiner, G.; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P. G. *J. Am. Chem. Soc.* **1994**, *116*, 11275−11286. The generality of this β-methylene-γ-butyrolactonization is currently being studied in our laboratory.

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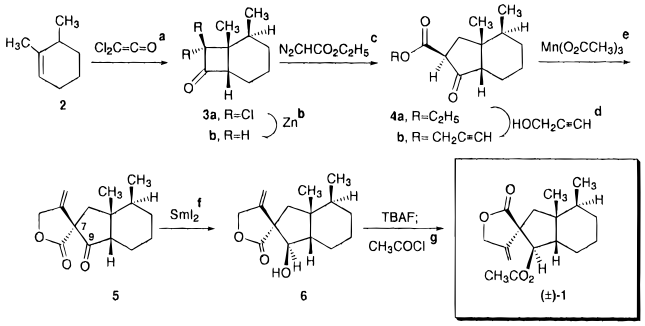
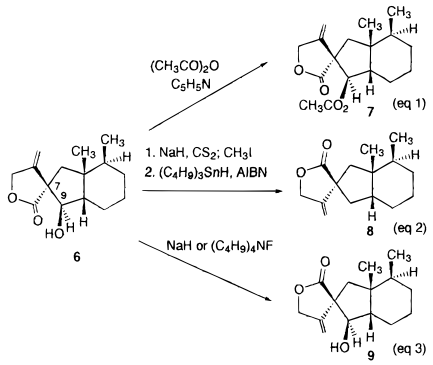
Scheme 1[a]



[a] (a) Reference 3c. (b) CH_3CO_2H, 70 °C, 3 h (63%, two steps). (c) $SbCl_5$, CH_2Cl_2, −78 → −30 °C, 12 h (64%). (d) *p*-TsOH, C_6H_6, reflux, 30 h. (e) C_2H_5OH, 20 °C, 2.5 h (61%, two steps). (f) THF−H_2O, 20 °C, 1 h (92%). (g) THF, 0 °C, 15 min; $(C_2H_5)_3N$, DMAP, THF, 20 °C, 48 h (60−70%).

completely ineffective. Fortunately, however, samarium diiodide proved remarkably efficacious and delivered a single hydroxy lactone (**6**), of unclear C-7, C-9 stereochemistry, in 92% yield.[11]

Although the derived acetate (**7**) displayed spectroscopic data quite similar to those reported for the natural product, there were nevertheless obvious discrepancies (eq 1). Since NOSEY



experiments proved inconclusive, the C-9 hydroxyl group was removed for the purpose of defining the stereochemistry at C-7 through correlation with bakkenolide A (**8**); misleadingly, bakkenolide A was indeed obtained (eq 2). At this point, fortunately, the long-sought authentic sample of the natural product was finally secured. The natural material on acid hydrolysis provided the corresponding hydroxy lactone, which, in turn, on PCC oxidation furnished the corresponding keto lactone. These two derivatives of the natural product were distinctly different from the synthetic compounds **6** and **5**, respectively. A single-crystal X-ray analysis of the dichloroacetate derivative of **6** (Figure 1a) indicated the stereochemistry to be in fact 7*R*(*S*), 9*S*(*R*).[12]

The only reasonable explanation for the above results was that a fortuitous retroaldol−aldol reaction during xanthate formation was generating the natural configuration at the C-7 diastereogenic center from epimeric material. *This was, in fact, the case: exposure of* ***6*** *in THF to sodium hydride, or better*

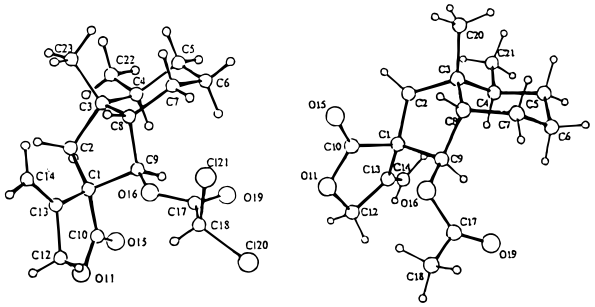


Figure 1. (a) Crystal structure of dichloroacetate of **6**. (b) Crystal structure of (±)-**1**.

tetrabutylammonium fluoride, yielded hydroxy lactone ***9*** *as the exclusive product,* in addition to some starting material (ca. 3.5:1, eq 3).[13] Molecular modeling of the four possible hydroxy lactone stereoisomers revealed, as now expected, **9**, with the natural relative stereochemistry at C-7, C-9, to have the lowest global minimum energy (followed by **6**).[14] The natural product, conceivably, also issues from such an equilibration process.

Preparatively, the transformation of hydroxy lactone **6** into 9-acetoxyfukinanolide could be conveniently accomplished in a single flask by addition of acetyl chloride and triethylamine directly to the retroaldol−aldol reaction medium. The product, so obtained in 60−70% yield, was indistinguishable on chromatographic and spectroscopic comparison from the authentic sample of the natural product. A single-crystal X-ray analysis of (±)-**1** (Figure 1b) served to corroborate the structure and relative stereochemical assignments[1d,g] for synthetic and natural 9-acetoxyfukinanolide.[15,16]

Work directed toward the synthesis of related bakkanes through application of this effective approach (**1** is obtained in seven steps and 15% overall yield) is currently being carried out in our laboratory. Preliminary results have shown that keto lactone **5** can be dehydrogenated to produce the $\Delta^{1(10)}$ derivative, which may prove to be a useful intermediate for the preparation of densely functionalized bakkanes such as fukinolidiol, homofukinolide, and the bakkenolides B−D.[17]

Acknowledgment. This paper is dedicated to Prof. Guy Ourisson on the occasion of his 70th birthday. We thank Profs. J. Lhomme and G. Mehta for their interest in our work, Prof. P. Sinäy and Dr. I. Gautier-Luneau for beneficial discussions, Ms. M.-L. Dheu-Andries and Dr. P. Vatton for their assistance with the molecular modeling, and Prof. M. Kawai, Prof. M. Noda, Ms. N. Pujol, and Mr. K. Watanabe for their considerable help in securing a sample of natural 9-acetoxyfukinanolide. Financial support from the CNRS (UMR 5616) and a fellowship award from the MESR to O. Hamelin are gratefully acknowledged.

Supporting Information Available: Complete experimental procedures with spectral and analytical data for the synthesis of (±)-**1** from cycloadduct **3a** and crystallographic data for (±)-**1** and the dichloroacetate derivative of (±)-**6** (21 pages). See any current masthead page for ordering and Internet access instructions.

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(10) Examination of the transition states leading to the two diastereomeric lactones was not sufficiently helpful to permit a confident assignment of the C-7 configuration.

(11) For reviews, see: Molander, G. A. *Org. React.* **1994**, *46*, 211−367. Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68. Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307−338. For a similar reduction problem and an alternative solution, see: Wang, T.-Z.; Pinard, E.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 1309−1318.

(12) Crystal data for the dichloroacetate derivative of (±)-**6**: $C_{17}H_{22}Cl_2O_4$, monoclinic, *P*21/*c*, a = 6.959(2) Å, b = 16.050(5) Å, c = 15.275(4) Å, β = 90.73(3)°, V = 1706.0(8) Å^3, Z = 4, d_{calcd} = 1.407 mg/m^3, $F(000)$ = 760, θ_{max} range 2.54−26.01°, 3641 measured reflections, 3369 [R(int) = 0.0277] independent reflections, $R(1)$ [$I > 2\sigma(I)$] = 0.0468, wR2 [all data] = 0.1063, GOF (all data) = 0.970 (1.147).

(13) For a related example, see: White, J. D.; Cutshall, N. S.; Kim, T.-S.; Shin, H. *J. Am. Chem. Soc.* **1995**, *117*, 9780−9781.

(14) Molecular modeling was performed on a Silicon Graphics MD25G workstation running Insight II Discover, version 2.3.0 (Biosym Technologies, San Diego). The structure was energy minimized with the force field cvff.frc. and the minimization algorithm VA09A. The diastereomer **9** was found to be 1.1 kcal/mol lower in energy than **6**.

(15) Crystal data for (±)-**1**: $C_{17}H_{24}O_4$, monoclinic, *P*21/*c*, a =11.391(3) Å, b = 12.003(3) Å, c = 11.799(2) Å, β = 102.01(2)°, V = 1577.9(6) Å^3, Z = 4, d_{calcd} = 1.231 mg/m^3, $F(000)$ = 632, θ_{max} range 3.97−67.48°, 2983 measured reflections, 2842 [R(int) = 0.0395] independent reflections, $R(1)$ [$I > 2\sigma(I)$] = 0.0467, wR2 [all data] = 0.1425, GOF (all data) = 1.101 (1.134).

(16) Since enantiomerically pure 1,6-dimethylcyclohexene (**2**) has been prepared in our laboratory,[3d] this work also constitutes, in a formal sense, the synthesis of natural 9-acetoxyfukinanolide.

(17) *Dictionary of Terpenoids*; Connolly, J. D., Hill, R. A., Eds.; Chapman and Hall: New York, 1991; Vol. 1, p 566 and references cited therein.