The stereochemistry of compounds **6**, **8**, and **10** was confirmed by NOE experiments. The structure of the β-functionalized compound **5** is not well defined due to its carbenoid nature, but its chemical behavior suggests a trans relationship for the lithium and the isopropoxy groups. Recently, we have prepared and characterized examples of 2-functionalized lithioalkanes which are rare and unstable species.[9] Some β-functionalized lithioalkenes have been reported,[10] but the trans compounds undergo β-elimination reactions except in a few cases in which a halogen is present in the α-position.[11]

The vinylic iodine present in compound **5** can undergo an exchange reaction with another organolithium reagent yielding the β-functionalized 1,1-dilithio-1-alkene. The consecutive treatment of a solution of **5a** with methyllithium[12] and conventional electrophiles affords the disubstitution products **16–20** (Scheme II).

The THF solutions of **15** are stable at −70 °C, and they give the same results shown in Scheme II upon treatment with electrophiles after 10 h at this temperature.

The yields and purities of compounds **3**, **6–13**, and **16–20** were determined by GC, and the spectral data (IR, ^{1}H NMR, ^{13}C NMR, and MS) are in accordance with the proposed structures.[13] The derivatives carrying an isopropoxy group are easily hydrolyzed to the corresponding carbonyl systems.[14]

Among all the products derived from lithioalkenes **5** and **15** we can emphasize the synthetic interest of the unconjugated diene **9**, the tetrasubstituted alkene **10**, the 1,2,3-trifunctionalized compounds **11** and **12** (with very different functional groups), the masked functionalized ketene **19** and the β-tricarbonyl compound **20**.

These results show the possibility of the preparation of β-functionalized 1-iodo-1-lithio-1-alkenes and 1,1-dilithio-1-alkenes and their use as synthons of the type RR′C=C< or RCOCH< after hydrolysis.

Acknowledgment. This work was supported by the Comisiõn Asesora de Investigaciõn Científica y Tẽcnica (CAYCIT, Spain). M.A.R. was supported by a Predoctoral Fellowship awarded by the Ministerio de Educaciõn y Ciencia, Spain.

Registry No. **1a**, 932-88-7; **1b**, 1119-67-1; **2**, 15656-28-7; **3a**, 115117-72-1; **3b**, 115117-47-0; **3c**, 115117-48-1; **3d**, 115117-49-2; **3e**, 115117-73-2; **3f**, 115117-50-5; **3g**, 115117-51-6; **3h**, 115117-52-7; **3i**, 115117-53-8; **3j**, 115117-54-9; **5a**, 115117-55-0; **5b**, 115117-56-1; **6**, 115117-57-2; **7**, 115117-58-3; **8**, 115117-59-4; **9**, 115117-60-7; **10**, 115117-61-8; **11**, 115117-62-9; **12**, 115117-63-0; **13**, 109000-22-8; **14**, 115117-64-1; (*Z*)-**14**, 115117-70-9; (*E*)-**14**, 115117-71-0; **15**, 115117-65-2; **16**, 42237-98-9; **17**, 115117-66-3; **18**, 115117-67-4; **19**, 115117-68-5; **20**, 115117-69-6; MeSSMe, 624-92-0; MeCHO, 75-07-0; Me_2NCHO, 68-12-2; *p*-iodoanisole, 696-62-8; *trans*-1,4-diphenyl-2-butene-1,4-dione, 959-28-4.

Supplementary Material Available: Experimental procedures for a typical preparation of **3** and the formation of **5** and **15** and their reactions with electrophiles (2 pages). Ordering information is given on any current masthead page.

(9) Barluenga, J.; Fañanãs, F. J.; Yus, M.; Asensio, G. *Tetrahedron Lett.* **1978**, 2015–2016. Barluenga, J.; Fañanãs, F. J.; Villamaña, J.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2685–2692.

(10) See, for example: Huang, S. J.; Lessar, M. V. *J. Org. Chem.* **1970**, *35*, 1204–1206. Duhamel, L.; Poirier, J.-M. *J. Am. Chem. Soc.* **1977**, *99*, 8356–8357. Wollemberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365–7367. Ficini, J.; Falou, S.; Touzin, A.-M.; d'Angelo, J. *Tetrahedron Lett.* **1977**, 3589–3592. Lau, K. S. Y.; Schlosser, M. *J. Org. Chem.* **1978**, *43*, 1595–1598. Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C.; Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411–5412. Barluenga, J.; Fernãndez, J. R.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 203–204.

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(12) Different organolithium compounds were tried, but the best results were obtained with methyllithium.

(13) All the new compounds present satisfactory microanalyses (C, ±0.23; H, ±0.16).

(14) Enol ether (1 equiv) in acetonitrile and 4 equiv of HBF_4 (35% aqueous solution) were stirred at room temperature for 4 h.

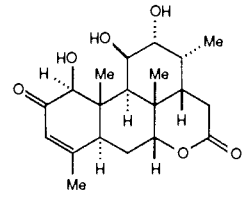
Total Synthesis of a Highly Oxygenated Quassinoid, (±)-Klaineanone

Paul A. Grieco,* David T. Parker,[1] and Ravi P. Nargund

Department of Chemistry, Indiana University Bloomington, Indiana 47405

Received April 18, 1988

A characteristic feature common to many naturally occurring quassinoids is the presence in ring A of a 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit bearing a methyl group at C(4) [cf. klaineanone (**1**)].[2]



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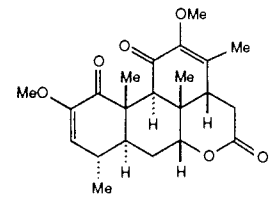

QUASSIN

This structural fragment is essential for the rich array of pharmacological properties associated with quassinoids.[3] Since the report describing the successful completion of the total synthesis of quassin in 1980,[4] there has not been a single published account detailing a total synthesis of a complex quassinoid. This is particularly surprising in view of the numerous synthetic groups worldwide who have been working on this problem for more than 15 years.[5] The lack of success to date has been in large part due to problems associated with elaboration of the ring A functionality.[6] Reported herein is the first total synthesis of a highly oxygenated quassinoid, (±)-klaineanone (**1**),[7] possessing the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality in ring A. It is of interest to note that of the ten stereocenters present in klaineanone, nine are contiguous.

The preparation of **1** commences with tetracyclic ketone **2** prepared previously[4] in connection with our synthesis of (±)-quassin. While compound **2** possesses all the carbon atoms needed for the construction of **1**, the configuration of C(9), which was established by a Diels–Alder strategy, requires inversion of configuration. Thus ketone **2** was transformed (92% yield) into enone **3**, mp 172.5–174.0 °C, via the corresponding $\Delta^{11,12}$ enol silyl ether via a two-step process involving reaction of the lithium enolate of **2** [LDA, THF, −78 °C (15 min) → 0 °C (1 h) → −78 °C] with 3.0 equiv of trimethylchlorosilane [−78 °C (30 min) → 0 °C (30 min)] and subsequent exposure (45 °C, 48 h) of the $\Delta^{11,12}$ enol silyl ether in acetonitrile to 1.3 equiv of palladium acetate and 4.0 equiv of sodium carbonate. Enone **3** was subjected to Birch reduction in liquid ammonia at −78 °C with 10 equiv of lithium metal in the presence of 0.9 equiv of *tert*-butyl alcohol. The resulting lithium enolate was trapped [0 °C (30 min) → room temperature (3 h)] with 3.0 equiv of diethyl phosphorochloridate in tetrahydrofuran-*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2:1) giving rise to enol phosphate **4**, mp 102.0–102.5 °C, in 80% overall

(1) Procter and Gamble Predoctoral Fellow, 1987–1988.

(2) For an excellent review on quassinoids, see: Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1985**, *47*, 22.

(3) Quassinoids possess a wide spectrum of biological properties including in vivo antileukemic, antiviral, antimalarial, antifeedant, amoebicidal, and insecticidal activity (Polonsky, J. "Chemistry and Biological Activity of the Quassinoids" In *The Chemistry and Chemical Taxonomy of the Rutales*; Waterman, P. G., Grundon, M. F., Eds.; Academic Press: New York, 1983; p 247. Lidert, Z.; Wing, K.; Polonsky, J.; Imakura, Y.; Okano, M.; Tani, S.; Lin, Y.-M.; Kiyokawa, H.; Lee, K.-H. *J. Nat. Prod.* **1987**, *50*, 442).

(4) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586. Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.

(5) Kim, M.; Gross, R. S.; Sevestre, H.; Dunlap, N. K.; Watt, D. S. *J. Org. Chem.* **1988**, *53*, 93. Kawabata, T.; Grieco, P. A.; Sham, H.-L.; Kim, H.; Jaw, J. Y.; Tu, S. *J. Org. Chem.* **1987**, *52*, 3346 and references cited therein.

(6) For synthetic methods addressing the problems associated with the construction of the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality present in ring A of quassinoids, see: McKittrick, B. A.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5897. Spohn, R.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491.

(7) Polonsky, J.; Bourguignon-Zylber, N. *Bull. Soc. Chim. Fr.* **1965**, 2793.

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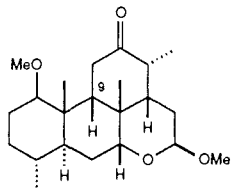

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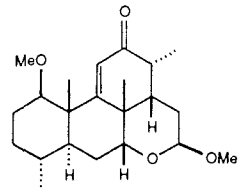

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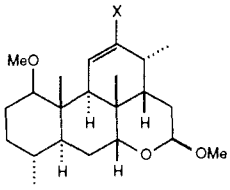
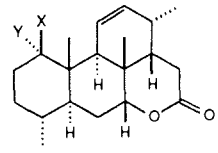


4 X = $OPO(OEt)_2$

5 X = H



6 X = OMe, Y = H

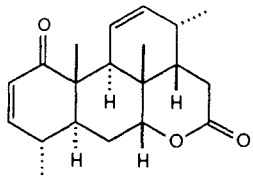
7 X = OH, Y = H

8 X = Y = O

yield. Reductive elimination [Li (100 equiv), $EtNH_2$, *t*-BuOH (1.0 equiv), THF] of the phosphate group proceeded smoothly affording tetracyclic olefin **5** in 92% yield.

Prior to elaboration of the ring A functionality, the protected lactol in **5** was converted in 77% overall yield into the tetracyclic lactone **6**, mp 174-176 °C, via a two-step sequence (1. 5% HCl, THF, 5 h; 2. Jones oxidation, 0 °C, 30 min). Cleavage of the methyl ether in compound **6** required prolonged exposure (70 h) of **6** to boron trifluoride etherate/ethanedithiol (1.0:1.7) containing a catalytic amount of concentrated hydrochloric acid in order to realize a 70% yield of crystalline tetracyclic alcohol **7**, mp 167.5-169.0 °C. Oxidation [PCC (3.0 equiv), NaOAc (2.5 equiv), CH_2Cl_2, 0 °C (30 min) → room temperature (30 min)] of **7** provided in 99% yield ketone **8**, mp 180.5-181.0 °C.

The required ring A functionality was introduced at this stage of the synthesis since all attempts to elaborate ring A in the presence of the C(11), C(12) trans diaxial vicinal diol unit failed. Tetracyclic ketone **8** was converted (82% yield) into enone **9**, mp 206.5-207.5 °C, via a three-step sequence involving enol silyl ether formation [HMDS (7 equiv), Et_3N (7 equiv), TMSI (5 equiv), $ClCH_2CH_2Cl$, -23 °C → room temperature (3 h)], trapping of the enol silyl ether with phenylselenenyl chloride in tetrahydrofuran at 0 °C (20 min), and oxidation (H_2O_2, pyridine, 0 °C, 1.5 h) of the corresponding keto selenide which underwent loss of benzene selenenic acid. Elaboration of the ring A functionality required transformation of enone **9** into the corresponding silyl dienol ether.



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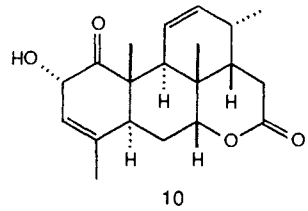
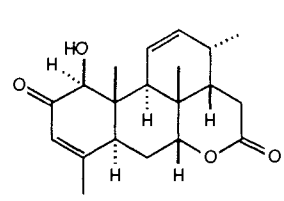
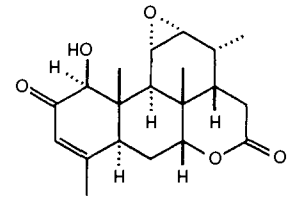


10

Toward this end, enone **9** was treated with 15 equiv of hexamethyldisilazane, 15 equiv of triethylamine, and 10 equiv of trimethylsilyl iodide in 1,2-dichloroethane initially at -23 °C and then at ambient temperature for 13 h. Peracid oxidation[8] [MCPBA (1.2 equiv), $NaHCO_3$ (1.5 equiv), CH_2Cl_2, -23 °C, 45 min] of the corresponding silyl dienol ether followed by treatment with 3.0 equiv of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran for 1 h at -23 °C provided, in 50% overall yield from **9**, tetracyclic α-hydroxy ketone **10**. Base-catalyzed tautomerism of **10** into **11**, mp 227-230 °C, was realized in 75% yield by treatment of a 0.02 M solution of **10** in methanol with 1.2 equiv of finely powdered potassium carbonate. Epoxidation [MCPBA, CH_2Cl_2, 0 °C (35 min) → room temperature (2.5 h)] of tetracyclic olefin **11** gave rise to crystalline



11



12

epoxide **12**, mp 217.5-219.5 °C, as the sole product in 80% yield. Acid-catalyzed opening of epoxide **12** with 23% perchloric acid in tetrahydrofuran-methylene chloride, 15:1, at ambient temperature (36 h) produced in 76% yield synthetic (±)-klaineanone (**1**), mp 234-239 °C, identical with an authentic sample by 500-MHz ^1H NMR, IR, and silica gel TLC analysis in several solvent systems.[9] Completion of the synthesis of **1** confirms the structural assignment put forth by Polonsky and Zylber[7] for klaineanone nearly 25 years ago. Since that time, the structure of **1** has rested upon limited spectroscopic data and its conversion into quassin. The synthesis of racemic klaineanone is noteworthy in that (a) the transformation of tetracyclic ketone **2** into **1** requires no protecting groups, (b) the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality is surprisingly stable (cf. **12** → **1**) contrary to reports in the literature, and (c) the base-catalyzed tautomerism of α-hydroxy ketone **10** into **11** proceeds with remarkable efficiency despite the opportunity for numerous undesired side products.

Acknowledgment. Generous support for this work from the National Cancer Institute, National Institutes of Health (Grant CA 28865), is gratefully acknowledged. The 500 MHz NMR instrument (Bruker 500) used in the above studies was purchased in part with funds provided by the National Institutes of Health (RR 02858) and the National Science Foundation (CHE 85-13707). We are grateful to Dr. Zev Lidert (Rohm and Haas) and Dr. Judith Polonsky (Gif-Sur-Yvette) for samples of natural klaineanone.

(8) Cf. Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599.

(9) All new crystalline compounds have been fully characterized by IR, ^1H NMR, and combustion analysis.

Spin Echo NMR of Cobalt Zeolite Catalysts: Control of Particle Size and Structure†

Zongchao Zhang‡ and Steven L. Suib*,‡,§

Department of Chemistry, University of Connecticut Storrs, Connecticut 06268
Department of Chemical Engineering and Institute of Materials Science, University of Connecticut, Storrs, Connecticut 06268

Y. D. Zhang, W. A. Hines, and J. I. Budnick

Department of Physics and Institute of Materials Science, University of Connecticut Storrs, Connecticut 06268

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Nuclear magnetic resonance (NMR) spectroscopy has recently become a powerful tool in the study of solid zeolite catalysts via magic angle spinning (MAS) procedures.[1] The ordering of Si^{4+} and Al^{3+} in zeolite frameworks and the effects of dealumination

† We thank the Office of Basic Energy Research, Division of Chemical Sciences of the Department of Energy for support of this research.

‡ Department of Chemistry.

§ Department of Chemical Engineering and Institute of Materials Science.

(1) (a) Fyfe, C. A. *Solid State NMR for Chemists*; CFC Press: Guelph, Ontario, Canada, 1986. (b) Fyfe, C. A.; Thomas, J. M.; Klinowski, J.; Gobbi, G. C. *Angew. Chem., Int. Ed. Engl.* **1982**, *22*, 259-275. (c) Newsam, J. M. *Science (Washington, D.C.)* **1986**, *231*, 1093-1099. (d) Sierra de Saldarriaga, L.; Saldarriaga, C.; Davis, M. E. *J. Am. Chem. Soc.* **1987**, *109*, 2686-2691.

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