Acknowledgment. This work was supported by the National Science Foundation (DMB-8613741). W.-D.W. is a recipient of a Feodor Lynen Fellowship from the Alexander von Humboldt Foundation. We thank L. Proniewicz for stimulating discussions.

Registry No. Fe(TPP)O_2, 88083-22-1; O_2, 7782-44-7; OFe(TPP), 84152-32-9; ^{18}O, 14797-71-8.

Synthesis of 2-Functionalized 1,1-Diiodo-1-alkenes. Generation and Reactions of 1-Iodo-1-lithio-1-alkenes and 1,1-Dilithio-1-alkenes

José Barluenga,* Miguel A. Rodríguez, and Pedro J. Campos

Departamento de Química Organometálica
Universidad de Oviedo, 33071-Oviedo, Spain

Gregorio Asensio

Departamento de Química Orgánica
Universidad de Valencia, 46010-Valencia, Spain

Received December 9, 1987
Revised Manuscript Received May 19, 1988

In recent years, 1,1-dilithio-1-alkenes have been the center of interest.[1,2] A few compounds of this class have been prepared,[1,3] but in all the cases the 1,1-dilithioalkenes were unfunctionalized. We report here the first preparation of a β-functionalized 1,1-dilithio-1-alkene and its precursor, a 1-iodo-1-lithio-1-alkene, by treatment of a 1,1-diiodo-1-alkene with organolithium compounds as well as some synthetic applications of these lithioalkenes. A general method for the synthesis of previously undescribed 2-substituted 1,1-diiodo-1-alkenes are also shown.

Examples of 1,1-diiodo-1-alkenes containing a function in 2-position are unknown,[4] but they could be appropriate antecedents for functionalized 1,1-dilithio-1-alkenes. This fact prompted us to study the reactivity of 1-iodoacetylenes **1**[5] toward bis(pyridine)iodine(I) tetrafluoroborate **2**,[6] since this reagent adds I^+Nu^- to internal acetylenes[7] and thus would lead to a general entry to 1,1-diiodo-1-alkenes **3**.

When the iodinating reagent **2** is allowed to react with 1-iodoacetylenes **1** and a wide variety of nucleophiles **4**, 2-substituted 1,1-diiodo-1-alkenes **3** are produced in good to very good yields (see eq 1 and Table I).

$$\underset{\mathbf{1}}{R\text{-}C{\equiv}C\text{-}I} + \underset{\mathbf{2}}{I(py)_2.BF_4} + \underset{\mathbf{4}}{Nu(NuH)} \longrightarrow \underset{\mathbf{3}}{(R)(Nu)C{=}CI_2} \qquad (1)$$

1a, R = Ph; **1b**, R = *n*-C_4H_9

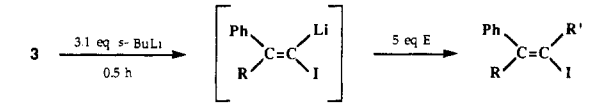
The reaction conditions are similar to the additions earlier mentioned.[7] These processes are clean, and, after the usual workup procedures, compounds **3** are obtained in more then 90% purity.

Table I. Synthesis of Compounds **3**

1	nucleophile	solvent	time[a] (h)	3	yield[b] (%)
a	$ClSiMe_3$	CH_2Cl_2	3	**a**[c]	65
a	Br^-	$MeCN/H_2O$	60	**b**	64
b	I^-	MeOH	14	**c**	70
a	NCS^-	dioxane/H_2O	60	**d**	75
a	pyridine	CH_2Cl_2	20	**e**	57
b	CH_3COOH	CH_3COOH/CH_2Cl_2 (2:1)	14	**f**	63
a	HCOOH	85% $HCOOH/CH_2Cl_2$ (2:1)	14	**g**	85
a	*i*-PrOH	*i*-PrOH/CH_2Cl_2 (2:1)	4	**h**	80
a	anisole	CH_2Cl_2	22	**i**[d]	50[e]
a	PhSH	CH_2Cl_2	15	**j**	80

[a] At room temperature except for the synthesis of **3a** and **3i** (−50 °C). [b] Yields of isolated products, relative to starting **2** and not optimized. [c] Structural formula (Ph)(Cl)C=CI_2. [d] Structural formula (Ph)(*p*-$CH_3OC_6H_4$)C=CI_2. [e] The crude reaction mixture contains 20% of *p*-iodoanisole.

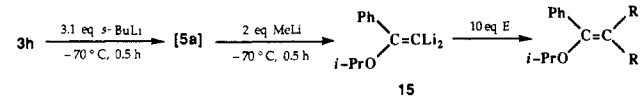
Scheme I



5

R = O*i*-Pr (−70 °C)	**5a**	E = MeOH	R' = H,	**6**	(70 %)
		D_2O	D,	**7**	(83 %)
		MeI	Me,	**8**	(65 %)
		CH_2=$CHCH_2Br$	CH_2=$CHCH_2$,	**9**	(58 %)
		MeSSMe	MeS,	**10**	(70 %)
		MeCHO	MeCHOH,	**11**	(57 %)
		Me_2NCHO	CHO,	**12**	(89 %)
R = *p*-$MeOC_6H_4$ (−105 °C)	**5b**	MeI	Me,	**13**	(57 %)

Scheme II



15

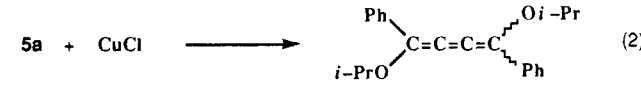
E = MeOH	R' = H,	**16**	(80 %)
D_2O	D,	**17**	(95 %)
MeI	Me,	**18**	(84 %)
MeSSMe	MeS,	**19**	(94 %)
$ClCO_2Et$	CO_2Et,	**20**	(70 %)

The synthetic potential of these new 2-functionalized 1,1-diiodo-1-alkenes by transformation of each iodine atoms is noteworthy. In this paper we describe the conversion of aromatic 1,1-diiodo-1-alkenes **3** to 1-iodo-1-alkenes and 1,1-dilithio-1-alkenes.

When compound **3** bearing an isopropoxy (**3h**) or a *p*-methoxyphenyl (**3i**) group in the 2-position is treated in THF with an excess of *sec*-butyllithium, a solution of the organolithium system **5** is obtained. The reaction of **5** with different electrophiles gives the corresponding monosubstituted products **6–13** (Scheme I).

The solution of **5a** is stable at −20 °C. Above this temperature it slowly begins to decompose, yielding the product **6** corresponding to abstraction of a solvent proton. At room temperature treatment of **5a** with an excess of iodomethane gives a complex mixture of **8**, **6**, and 1-isopropoxy-2-phenylacetylene (analyzed by ^{13}C NMR).

A solution of **5a** in the presence of cuprous chloride (3 equivs) at −60 °C is quantitatively transformed in 1,4-diisopropoxy-1,4-diphenyl-1,2,3-butatriene (**14**)[8] in 2 h (eq 2).



(2)

14

(1) Maercker, A.; Theis, M. *Top. Curr. Chem.* **1987**, *138*, 1–61.
(2) Apeloig, Y.; Schleyer, P. R.; Binkley, J. S.; Pople, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 4332–4334. Nagase, S.; Morokuma, K. *J. Am. Chem. Soc.* **1978**, *100*, 1661–1666. Laiding, W. D.; Schaefer, H. F. *J. Am. Chem. Soc.* **1979**, *101*, 7184–7188.
(3) Morrison, J. A.; Chung, C.; Lagow, R. J. *J. Am. Chem. Soc.* **1975**, *97*, 5015–5017. Maercker, A.; Dujardin, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 224. Maercker, A.; Dujardin, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 571–572.
(4) Gaviña, F.; Luis, S. V.; Ferrer, P.; Costero, A. M.; Marco, J. A. *J. Chem. Soc., Chem. Commun.* **1985**, 296–297.
(5) Barluenga, J.; González, J. M.; Rodríguez, M. A.; Campos, P. J.; Asensio, G. *Synthesis* **1987**, 661–662.
(6) Barluenga, J.; González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 319–320.
(7) Barluenga, J.; Rodríguez, M. A.; González, J. M.; Campos, P. J.; Asensio, G. *Tetrahedron Lett.* **1986**, *27*, 3303–3306.

(8) Compound **14** is a stable yellow solid (mp 105–107 °C, MeOH) corresponding to a single diastereoisomer but at 60 °C in methanol is converted in a cis–trans mixture (1:1). Its spectral data (IR, ^1H and ^{13}C NMR, and MS) and the acidic hydrolysis to *trans*-1,4-diphenyl-2-buten-1,4-dione are in accordance with the proposed 1,2,3-butatrienic structure.

0002-7863/88/1510-5567$01.50/0

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 Comisiôn Asesora de Investigaciôn Científica y Têcnica (CAYCIT, Spain). M.A.R. was supported by a Predoctoral Fellowship awarded by the Ministerio de Educaciôn 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.; Fañanás, F. J.; Yus, M.; Asensio, G. *Tetrahedron Lett.* **1978**, 2015–2016. Barluenga, J.; Fañanás, 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.; Fernández, J. R.; Yus, M. *J. Chem. Soc., Chem. Commun.* **1985**, 203–204.

(11) Ficini, J.; Depezay, J.-C. *Tetrahedron Lett.* **1968**, 937–942. Smithers, R. H. *J. Org. Chem.* **1983**, *48*, 2095–2097.

(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.

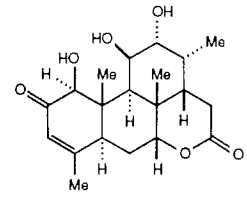
Total Synthesis of a Highly Oxygenated Quassinoid, (±)-Klaineanone

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

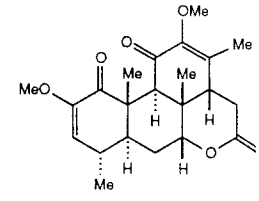
Department of Chemistry, Indiana University Bloomington, Indiana 47405

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]



1



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.

0002-7863/88/1510-5568$01.50/0