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Communications

Applications of Metalated Cyclopropenone Ketals in a General Synthesis of Cyclopropenones. An Efficient Synthesis of the Antibiotic Penitricin

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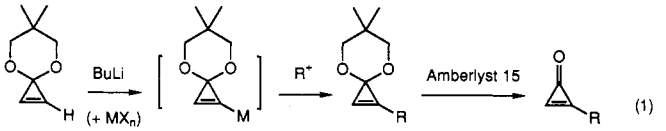
Summary: A variety of substituted cyclopropenones, including the antibiotic penitricin and its congeners, have been synthesized by a two-step sequence which involves the reaction of metalated cyclopropenone ketals with electrophiles.

Sir: Although cyclopropenones have attracted a great deal of attention from chemists in the past 30 years,[1] only a limited range of substituted derivatives (typically 2,3-diaryl compounds) have been studied due to the lack of general methods for the synthesis of this interesting class of compounds.[2] In this paper, we describe the chemistry of a new organometallic species **2** and its application in a new, versatile synthesis of substituted cyclopropenones. We also report the first practical synthesis of the cyclopropenone antibiotic penitricin (**7**: R^1, R^2 = H, Table I). Penitricin,[3] isolated from *Penicillium aculeatum* NR 5165, represents a novel, synthetically challenging structural class of cyclopropenones[4] whose mode of action is unknown. We describe the generation and the reactions of metalated cyclopropenone ketals **2** which serve not only as unique synthons for "cyclopropenone enolates" but as synthetically useful three-carbon nucleophiles as well.

Our strategy for the synthesis of 2-substituted and 2,3-disubstituted cyclopropenones is outline in eq 1. Treatment of the cyclopropenone ketal **1** (available in one step from a 1,3-dihaloacetone ketal in 77% yield)[5] with BuLi in THF at −70 °C results in remarkably clean lithiation[6] to afford an unstable lithiocyclopropene **2a**, which can be stabilized by the addition of 1.5–3 equiv of HMPA or TMEDA.[7] The reaction of this reagent with a variety of



(1)

1 **2** **3** **4**

a: M = Li,
b: M = 1/2 Zn(II)

electrophiles produces substituted cyclopropenes **3**, which can be hydrolyzed (Amberlyst 15, acetone) to the corresponding cyclopropenones **4** in good overall yield.[8] Table I summarizes our results. A variety of monoalkylcyclopropenones including an intriguing biscyclopropenone (entry 5) have been prepared in high yield through al-

(1) (a) Breslow, R.; Haynie, R.; Mirra, J. *J. Am. Chem. Soc.* **1959**, *81*, 247. (b) Volpin, M. E.; Koreshkov, Y. D.; Kursanov, D. N. *Izv. Akad. SSSR* **1959**, 560.

(2) Review: Potts, K. T.; Baum, J. S. *Chem. Rev.* **1974**, *74*, 189. Eicher, T.; Weber, J. L. *Top. Curr. Chem.* **1975**, *57*, 1.

(3) (a) Okuda, T.; Yoneyama, U.; Fujiwara, A.; Furumai, T. *J. Antibiot.* **1984**, *37*, 712. (b) Okuda, T.; Yokose, K.; Furumai, T.; Maruyama, H. B. *J. Antibiot.* **1984**, *37*, 718. (c) Okuda, T.; Shimma, N.; Furumai, T. *J. Antibiot.* **1984**, *37*, 723.

(4) For two other natural cyclopropenones, see: Bohlmann, F.; Jakupovic, J.; Mueller, L.; Schuster, A. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 292.

(5) Baucom, K. B.; Butler, G. B. *J. Org. Chem.* **1972**, *37*, 1730. Breslow, R.; Pecorara, J.; Sugimoto, T. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 361. Boger, D. L.; Brotherton, E.; Georg, G. I. *Org. Synth.* **1987**, *65*, 32.

(6) Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **1963**, *85*, 99.

(7) In the absence of the polar additives, **2a** undergoes rapid decomposition above −40 °C to give a complex mixture of products. In addition, HMPA greatly accelerates the alkylation reactions.

(8) (a) Butylation of **2a**: To a solution of **1** (10.0 mmol) and HMPA (25 mmol) in 15 mL of THF at −70 °C was added *n*-BuLi in hexane (6.02 mL, 10.5 mmol) over 10 min and then BuI (12.0 mmol) after 20 min. After 12 h at −70 °C, the reaction was quenched by addition of a pH 7 phosphate buffer. Purification on silica gel afforded 1.72 g (87%) of 2-butylcyclopropenone ketal. (b) Vinylation of **2b**: To a solution of **2a** (3.6 mmol) was added $ZnCl_2$ (1.8 mmol) in THF at −70 °C. *cis*-1-Hexenyl iodide (3.0 mmol) and $Pd(Ph_3P)_4$ (0.15 mmol) were added at 20 °C, and the mixture was stirred for 2.5 h: yield 570 mg, 85%. (c) Cyclopropenones: To a solution of the above vinylated ketal (1.0 mmol) in acetone (10 mL) was added 30 mg of Amberlyst 15, and the mixture was stirred for 40 min at 20 °C and then filtered. Addition of 30 μL of Et_3N followed by purification on silica gel afforded 122 mg of the desired cyclopropenone (90%).

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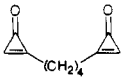
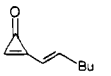
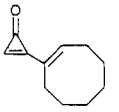
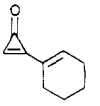
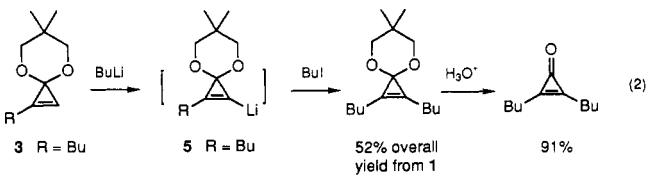
Table I. Preparation of Cyclopropenones by Alkylation of Metalated Cyclopropenone Ketals 2[a]

entry	2 (equiv)	alkylation: electrophile (equiv)	alkylation: % yield	cyclopropenone: % yield	cyclopropenone
		RX =			
1	**2a** (1)	MeI (1.05)	85, 94[c]	–[b]	 4: R = Me
2	**2a** (1)	BuI (1.2)	87	93	4: R = Bu
3	**2a** (1)	BuBr (2)	(91)	93	4: R = Bu
4	**2a** (1)	$Me_3SiC{\equiv}C(CH_2)_3I$ (1.1)	76	96	4: R = $(CH_2)_3C{\equiv}CSiMe_3$
5	**2a** (2.5)	$I(CH_2)_4I$ (1)	82	78	
6	**2b** (1.5)	*trans*-BuCH=CHI (1)	93	84[94][d]	
7	**2b** (1.2)	*cis*-BuCH=CHI (1)	87	99[e]	
8	**2b** (1.2)	1-cyclooctenyl iodide (1)	95	92	
9	**2b** (1.5)	1-cyclohexenyl triflate (1)	83	80	
10	**2b** (1.5)	C_6H_5I (1)	73	93	4: R = C_6H_5
11	**2b** (1.2)	*p*-$MeOC_6H_4I$ (1)	79	92	4: R = *p*-$MeOC_6H_4$
		R^1COR^2 =			
12	**2a** (1)	HCHO[f]	51	71 (94)	 7: R^1, R^2 = H
13	**2a** (1.1)	$CH_3(CH_2)_6CHO$ (1)	85	80	7: R^1 = H, R^2 = C_7H_{15}
14	**2a** (1)	C_6H_5CHO (1.1)	93	88	7: R^1 = H, R^2 = C_6H_5
15	**2a** (1.1)	cyclohexanone (1)	92	91	7: R^1, R^2 = $-(CH_2)_5-$

[a] The reactions were carried out as described in ref 7. Yields are based on pure isolated material except when noted otherwise. NMR yield in parentheses. [b] Deprotection was not attempted. [c] GLC yield using an internal standard. [d] Yield based on conversion. [e] A trace amount (3%) of trans isomer formed. [f] Five equiv of paraformaldehyde was pyrolyzed at 160–170 °C and introduced to a solution of **2a** in THF at –40 °C.

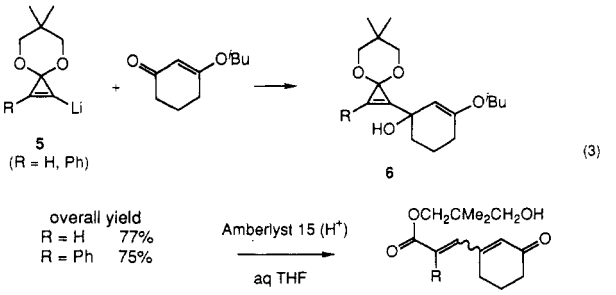
kylation of **2a** with alkyl halides (entries 1–5). The zinc reagent **2b** generated by the reaction of **2a** with 0.5 equiv of $ZnCl_2$[7b] has been found to be stable even at room temperature, and has proven to be particularly suitable for reactions with alkenylating and arylating agents. Thus, the stereospecific $Pd(Ph_3P)_4$-catalyzed reaction[9] of **2b** with vinyl halides and triflates followed by hydrolysis afforded, in high overall yield, the previously inaccessible intriguing monovinylcyclopropenones shown in entries 6–9. Coupling of **2b** with aryl iodides can be performed in an identical manner to obtain 1-arylcyclopropenones in good overall yields (entries 10 and 11). The application of the method to the synthesis of 2,3-disubstituted cyclopropenones is illustrated in eq 2.



(2)

The reaction of **2a** with formaldehyde gas (entry 12) provides an efficient synthetic route to the antibiotic penitricin (7, R^1, R^2 = H; 40–50% overall yield, ca. 1% in the previous synthesis[3c]). Similarly, the reaction of **2a** with a variety of carbonyl compounds affords substituted analogues (entries 13–15), many of which have much longer shelf-lives than the parent compound, while often possessing stronger antibiotic activities.[10] Efficient access to a variety of derivatives should facilitate the biochemical investigation of this intriguing class of antibiotics.

Besides their utility for the synthesis of cyclopropenones, we expect that metallocyclopropenone ketals will find use in a variety of useful synthetic transformations. For instance, in eq 3, **5** acts as a homoenolate-like synthon, wherein acidic treatment of the adduct **6** unravels a latent



(3)

(9) Cf.: Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298.

(10) Minimum inhibitory concentrations (μg/mL) of compounds in entries 13 and 15 against selected test organisms are compared with that of penitricin (7, R^1, R^2 = H): *K. pneumonia* PCI-602 (25, 50, 33 in the above order), *P. morganii* IFO 3848 (12.5, 50.33), *B. subtilis* ATCC 6633 (50, 100, 100), *M. luteus* ATCC 9341 (50, 100, 33).

acrylate structure in **5**. In addition, we anticipate that thermal[11,12] and organometallic[13] reactions of the substituted cyclopropenone ketals (e.g., **3**) will provide exciting new fields of future research.

(11) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695 and references therein.
(12) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.*, in press.
(13) Nakamura, E.; Isaka, M.; Matsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297.

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Supplementary Material Available: Physical properties of cyclopropenones (7 pages). Ordering information is given on any current masthead page.

Synthesis and Absolute Configuration of (−)-Furodysinin. New Transformations of Camphor Derivatives

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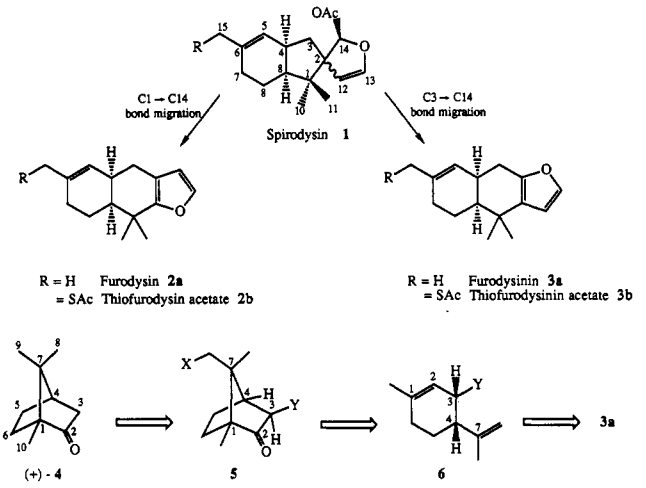
Summary: The synthesis of (−)-furodysinin ((−)-**3a**) has been accomplished in five steps from (+)-π-bromocamphor (**7**) and has allowed assignment of the absolute configuration of a number of marine furanosesquiterpenes produced by sponges of the genus *Dysidea*.

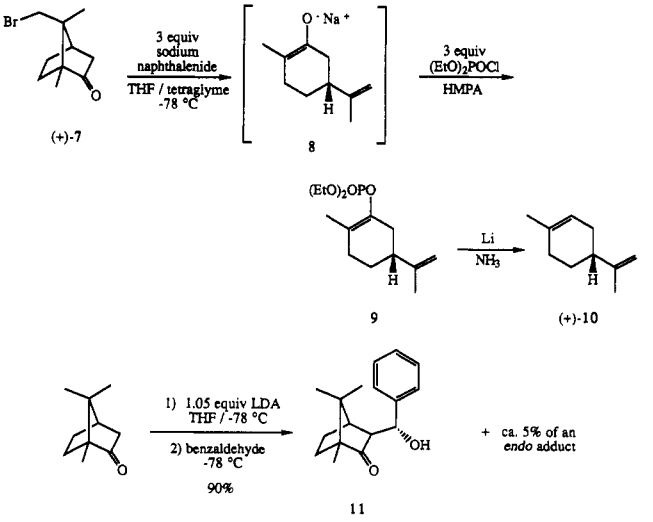
Sir: Tropical sponges of the family Dysideidae are sources of a wide variety of secondary metabolites including polybrominated diphenyl ethers, amino acid derived substances, and a variety of terpenes.[1,2] In particular, the Indo-Pacific sponge *Dysidea herbacea* elaborates furanosesquiterpenes of many skeletal types.[3] Among these are the tricyclic compounds shown in Scheme I that were originally isolated and described by Wells and co-workers in 1978.[4] Furodysin (**2a**), furodysinin (**3a**) and their thioacetyl analogues have been shown to arise by solvolysis and cationic rearrangement of spirodysin (**1**), a cometabolite found in this species. The relative configurations of the compounds were determined spectroscopically and by use of X-ray crystallography. Although the absolute configurations of **1–3** have not been determined, it is interesting that both enantiomers of **3a** have been detected in the same sponge genus from sources only 1500 miles apart.[5,6] It is reasonable to assume that **2** and **3** arise in the sponge from **1**. In a general approach to metabolites **2–3** among others, we have expanded the versatile chemistry of camphor[7] to achieve a concise synthesis[8] of (−)-furodysinin from (+)-camphor (**4**) thus establishing the absolute configuration of this series of sponge metabolites.

Our general strategy (Scheme I) was to derivatize camphor prior to cleavage of the C1–C7 bond, which establishes the eventual cis junction of the bicyclo[4.4.0] ring system. Two model studies established the viability of our approach (Scheme II). In the first model, a fragmentation of the bicyclo[2.2.1] ring system[9] was achieved by treating (+)-9-bromocamphor (**7**) with 3 equiv of sodium naphthalenide in THF at −78 °C, presumably resulting in the regiospecifically generated enolate **8**, which was trapped with diethyl chlorophosphate to give the enol phosphate **9** in 80% yield. Dissolving metal reduction of **9** led to (+)-limonene (**10**) in 80% yield, thus allowing camphor to be used as a six-membered chiral pool element. The exo alkylation of camphor at the 3-position must also be

Scheme I



Scheme II



achieved to utilize this process for the production of **2–3**. In a surprising development, the desired exo alkylation of

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(1) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1–34.
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