Reaction of Tin Enolates with Substituted Tricarbonylcyclohexadienyliumiron Hexafluorophosphate Electrophiles: Diastereoselective Synthesis of (±)-Trichodiene

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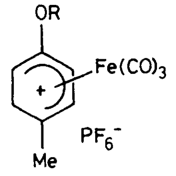
A number of tin enolates react cleanly with tricarbonylcyclohexadienyliumiron cations, in cases where the use of lithium enolates or silyl enol ethers is problematic; this new carbon–carbon bond-forming reaction allows diastereoselective construction of proximate quaternary centres and provides a key step in a short synthesis of (±)-trichodiene.

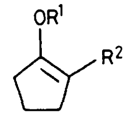
We have previously reported the total synthesis of several trichothecene analogues[1] in which the initial carbon–carbon bond-forming step involved reaction between a stabilized metal enolate (**3a**) and tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (**1**). These syntheses suffer from two serious drawbacks. First, reduction of the methyl ester group of (**6**) to a saturated methyl group has proven prohibitively difficult, denying access to natural products such as trichodermol[2] and verrucarol.[3] Secondly, the initial step is non-diastereoselective, giving equimolar mixtures of diastereoisomers (**6A** and **B**) which must be separated. Since it has been demonstrated that certain silyl enol ethers successfully add regio- and stereo-specifically to the dienyl terminus of selected tricarbonylcyclohexadienylium iron hexafluorophosphate electrophiles,[4] while *stabilized* metal enolates have been shown to add in the same manner to the methyl-substituted terminus of (**1**) (Scheme 1), it was hoped that *unstabilized* metal enolates substituted at the α-position, or the analogous *O*-trimethylsilyl enols, could be induced to add to (**1**). While the *O*-trimethylsilylenol (**3b**) of cyclopentanone in our hands reacts with (**1**) to give good yields of (**7A** and **B**) (69%), substituted *O*-silyl enols such as 1-trimethylsilyloxy-2-methylcyclopentene (**3c**) prove unreactive. Unstabilized metal (particularly lithium) enolates such as (**3d**), on the other hand, are too basic, deprotonating the methyl group to give compound (**9**).

In this communication, we describe the utilization of cyclic and acyclic tri-n-butyltin enolates (generated *in situ* from corresponding *O*-silyl enols[5]) as an excellent means of effecting C–C bond formation in systems where lithium enolates and silyl enol ethers are useless.

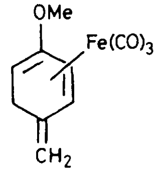
Table 1 contains a representative sample of the nucleophiles and electrophiles employed. Utilization of tin enolates results in diastereoselectivities not hitherto encountered with metal enolates and *O*-silyl enols. The results in entry 2 are of particular interest, since the simultaneous formation of two contiguous quaternary centres in high yield with diastereoselectivity has been effected (a difficult transformation by standard organic methodology). Moreover, the major isomer (**8A**) possesses the carbon skeleton and stereochemistry required for a four-step synthesis of the sesquiterpene



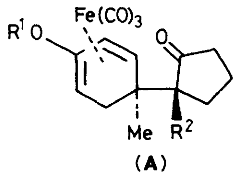
(**1**) R = Me
(**2**) R = Pr^i



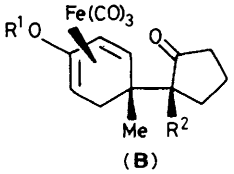
(**3**) a; R^1 = Na, R^2 = CO_2Me
b; R^1 = $SiMe_3$, R^2 = H
c; R^1 = $SiMe_3$, R^2 = Me
d; R^1 = M^+(Na, Li, K), R^2 = Me
e; R^1 = $SnBu_3$, R^2 = H
f; R^1 = $SnBu_3$, R^2 = Me



(**9**)

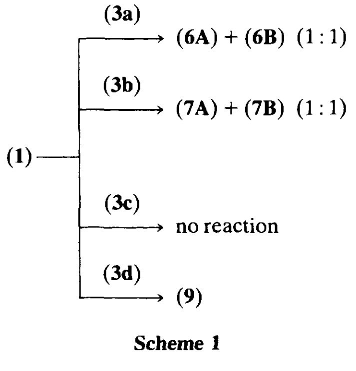


(**A**)



(**B**)

(**6**) R^1 = Me, R^2 = CO_2Me
(**7**) R^1 = Me, R^2 = H
(**8**) R^1 = Me, R^2 = Me

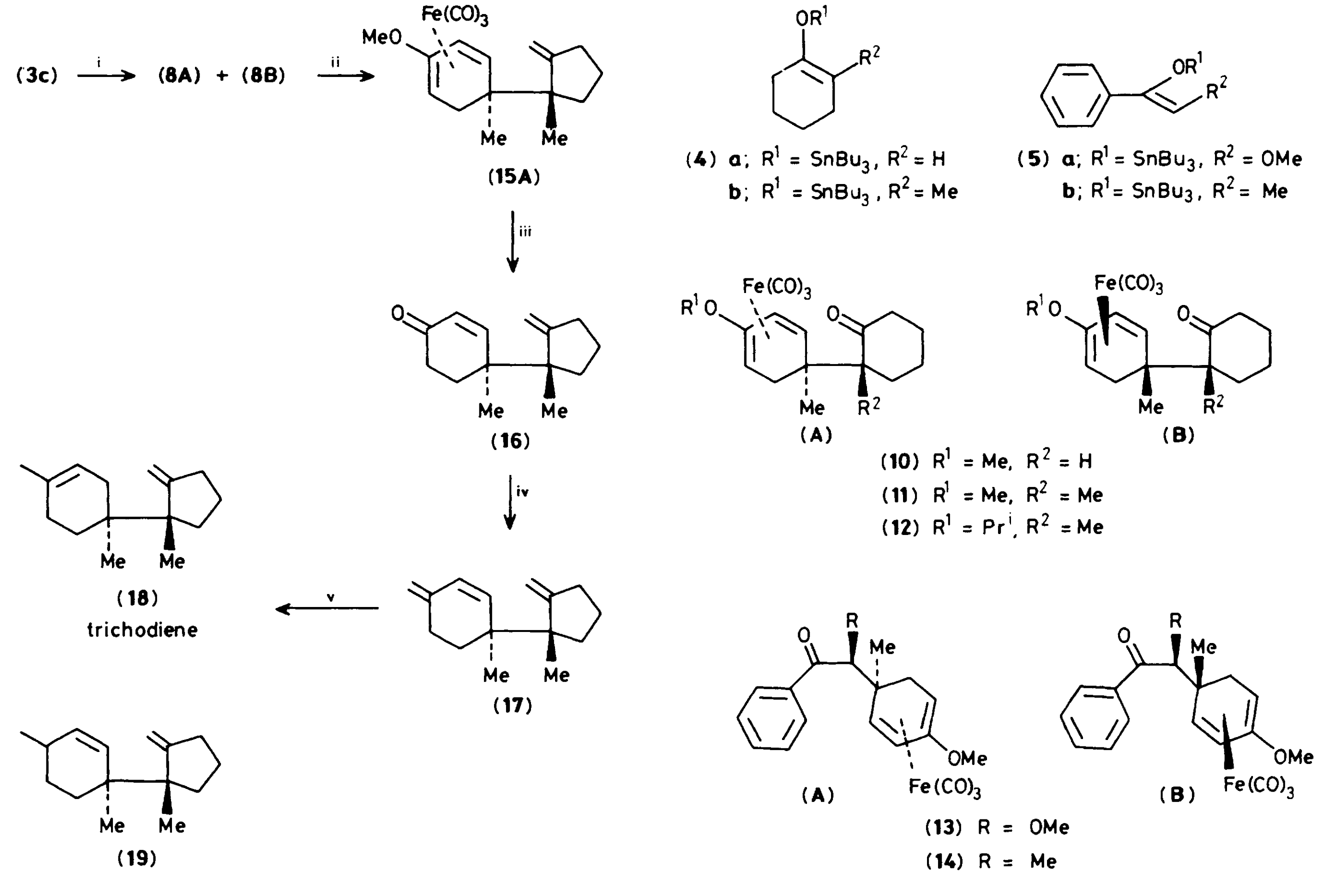


Scheme 1

Table 1. Reactions of tin enolates with dienyliumiron electrophiles.

Entry	Electrophile	Nucleophile[a]	Products[b]	Yield (%)	Diastereoselectivity (A : B)[c]
1	**(1)**	**(3e)**	**(7A + B)**	83	5 : 7
2	**(1)**	**(3f)**	**(8A + B)**	87	5 : 1
3	**(1)**	**(4a)**	**(10A + B)**	64	2 : 1
4	**(1)**	**(4b)**	**(11A + B)**	6.5	3 : 1
5	**(2)**	**(4b)**	**(12A + B)**	22	2 : 1
6	**(1)**	**(5a)**	**(13A + B)**	70	1 : 1
7	**(1)**	**(5b)**	**(14A + B)**	47	1 : 1

[a] Generated *in situ* from the corresponding *O*-silyl enols (see Scheme 2). [b] All products were fully characterized by n.m.r., i.r., and mass spectrometry and/or elemental analysis. [c] Determined by 200 MHz ^1H n.m.r. spectroscopy.



Scheme 2. *Reagents:* i, (a) MeLi, $(MeOCH)_2$, room temp., 30 min, (b) −78 °C, Bu_3SnCl, 30 min, (c) (**1**), MeCN, warm to −44 °C, 1 h; ii, $Ph_3P{=}CH_2$ (5 equiv. over 3 days), Et_2O, Bu^tOH; iii, $CuCl_2$, EtOH, room temp., 12 h; iv, $Ph_3P{=}CH_2$ (4 equiv.), Et_2O, Bu^tOH, 4 h; v, (a) Na, liq. NH_3, THF, −78 °C, 25 min, (b) abs. EtOH (excess).

hydrocarbon (±)-trichodiene (described herein). The stereochemistry of each isomer of (**8**) was assigned by comparison of n.m.r. spectral data with those of similar compounds previously characterized in our laboratory by *X*-ray crystallography.[6] Not surprisingly, the reaction between (**1**) and the tin enolate of 2-methylcyclohexanone (entry 4) was low yielding, but use of tricarbonyl(4-isopropoxy-1-methylcyclohexadienylium)iron hexafluorophosphate (**2**) in place of (**1**) results in higher yields (22%) presumably due to steric effects.[7]

The sesquiterpene hydrocarbon trichodiene is the biosynthetic precursor of the trichothecenes, a class of over eighty fungal metabolites.[8] Although several syntheses of trichodiene have been reported,[9] most involve separation of a *ca.* 50:50 mixture of diastereoisomers at some stage.[10] To demonstrate the applicability of this novel organoiron chemistry, a synthesis of (±)-trichodiene was undertaken that is highly diastereoselective and is unique in its approach to the formation of contiguous quaternary centres. Scheme 2 illustrates the sequence employed.

Olefination of (**8A** and **B**), by a modification of a procedure employed by Raphael,[11] resulted in a 53% yield of the single diastereoisomer (**15A**) after purification by flash chromatography. Trial experiments showed that decomplexation of (**8A**) with Me_3NO, followed by mild acidic hydrolysis of the enol ether, resulted in mixtures of enone and a bicyclic byproduct (due to an internal aldol condensation); thus olefination prior to decomplexation utilizes the iron tricarbonyl moiety as a protecting group. Oxidation of (**15A**) with $CuCl_2$ led directly to the enone (**16**) in quantitative yield, setting the stage for a second olefination to give the triene (**17**) in 98% yield. Finally, a dissolving metal reduction of (**17**) (Na, liq. NH_3, THF) resulted in a 70% yield of a 5:1 mixture of trichodiene (**18**) and the 1,2-reduction product (**19**). Separation was effected *via* preparative t.l.c. (12.5% $AgNO_3$-impregnated silica gel, 0.5% ether/hexane as eluent; trichodiene appeared as a fast-running band) to give pure trichodiene, having spectral characteristics identical with those previously reported.[8,9]

We are grateful to the U.S. Public Health Service, National Institutes of Health, for generous financial support of our research program.

Received, 12th May 1987; Com. 639

References

1 A. J. Pearson and Y. S. Chen, *J. Org. Chem.*, 1986, **51**, 1939; A. J. Pearson, *J. Chem. Soc., Chem. Commun.*, 1977, 339; *J. Chem. Soc., Perkin Trans. 1*, 1977, 2069.

2 W. C. Still and M. Y. Tasi, *J. Am. Chem. Soc.*, 1980, **102**, 3754.

3 W.R. Roush and T. F. D'Ambra, *J. Org. Chem.*, 1980, **45**, 3927; R. H. Schlessinger and R. A. Nugent, *J. Am. Chem. Soc.*, 1982, **104**, 116.

4 A. J. Birch, L. F. Kelly, and A. S. Narula, *Tetrahedron*, 1982, **38**, 1813.

5 Y. Yamamoto, H. Yatagai, and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1981, 162.

6 A. J. Pearson and P. R. Raithby, *J. Chem. Soc., Perkin Trans. 1*, 1980, 395.

7 A. J. Pearson, P. Ham, C. W. Ong, T. R. Perrior, and D. C. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1527.

8 Selected reviews: (a) P. G. McDougal and R. N. Schmuff, *Prog. Chem. Org. Nat. Prod.*, 1985, **47**, 153; (b) C. J. Miroca, S. V. Pathre, and C. M. Christenson, 'Mycotoxic Fungi, Mycotoxins, Mycotoxicoses,' Dekker, New York, 1977, vol. 1, pp. 365—409; (c) S. V. Pathre and C. J. Mirocha, *J. Am. Oil Chem. Soc.*, 1979, **56**, 820.

9 G. A. Kraus and P. J. Phomas, *J. Org. Chem.*, 1986, **51**, 503 and references cited therein; J. C. Gilberg and J. A. Kelly, *ibid.*, p. 4485; F. L. Middlesworth, *ibid.*, p. 5019; Minora Sudal, *Tetrahedron Lett.*, 1982, **23**, 427; S. C. Welch, A. S. C. Prakasa Rao, C. G. Gibbs, and R. Y. Wong, *J. Org. Chem.*, 1980, **45**, 4077.

10 For a diastereoselective synthesis of trichodiene, see K. E. Harding and K. S. Clement, *J. Org. Chem.*, 1984, **49**, 3870.

11 R. A. Raphael, E. W. Colvin, S. Malchenko, and J. S. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1989.