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Cyclohexenones as Michael Acceptors in the Staunton–Weinreb Annulation: A Simple Stannane Modification for the Synthesis of Polycyclic Systems

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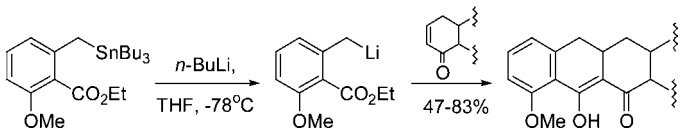
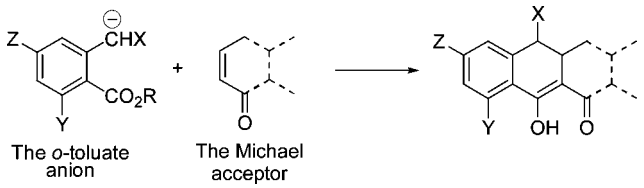
ABSTRACT



***o*-Toluate anions generated via transmetalation from the corresponding tributyl stannane underwent a Michael addition–Dieckmann condensation sequence with various cyclohexenones. This protocol provides an efficient entry into complex polycyclic systems without the use of *β*-alkoxy enones hitherto required for the reaction.**

The condensation of *o*-toluate anions with various Michael acceptors has been a useful protocol for the synthesis of polycyclic natural products. The scope and limitations of this attractive annulation (Scheme 1) were established by the pioneering research of Hauser,[1] Staunton,[2] and Weinreb.[3]

Scheme 1



An absolute requirement for the toluate was the presence of a substituent (usually OMe) at the Y position. Without it, rapid dimerization[1] of the anion (X = Y = H) took place. Additional methoxy groups were tolerated (e.g., Y = Z = OMe, X = H) and the ester could be varied[2] (R = Me, Et, Ph). A logical modification was the installation of an anion-stabilizing group (X = SPh, SOPh, SePh, SeOPh), but these substrates required an extra two or three steps for their preparation.[4] The stabilized anions were generated with lithium *tert*-butoxide[5] but the others (X = H) required LDA/THF at −78 °C. Many examples of the addition of stabilized *phthalide* anions to Michael acceptors are known[6] but a discussion of those reactions is beyond the scope of this paper.

Michael acceptors hitherto employed included α- and *γ*-pyrones, pyrylium salts,[7] α,*β* unsaturated esters,[8] and

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(1) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178.
(2) Carpenter, A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1043 and pertinent references therein.
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(7) Leeper, F. J.; Staunton, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1053.
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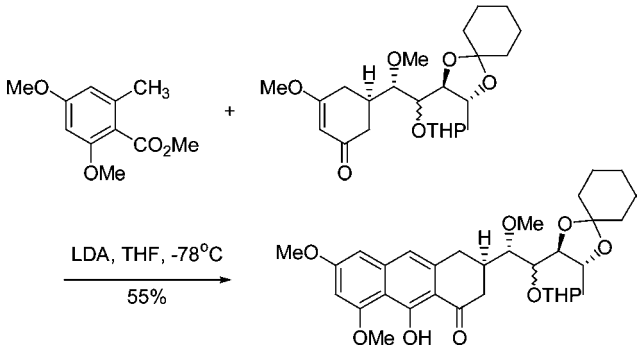
lactones. Yields were satisfactory and many polyketides were efficiently synthesized from methyl orsellinate[7,9] (X = H, Y = Z = OMe, R = Me). The reaction failed, however, with simple cyclohexenone acceptors even when stabilized toluate anions were employed.[1,3] Extensive polymerization of the enone occurred and the aromatic reactant was recovered unchanged. To remedy these adverse results, the cyclohexenone acceptor was modified by the introduction of a β-alkoxy group (methyl or ethyl) to effectively alter it to a vinylogous ester.[3] In common with the earlier successful reactions with lactones this strategy worked well and a three-step, "one-pot", Michael addition−Dieckmann condensation−aromatization sequence providing tricyclic products in gratifying overall yields.

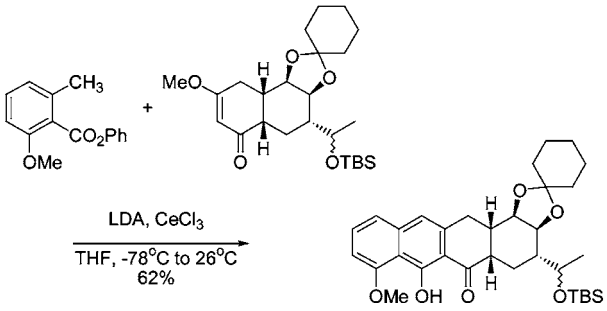
The same principle of β-alkoxylation as a device to minimize cyclohexenone polymerization was applied to the synthesis of olivin tri-*O*-methyl ether[10] and subsequently[11] to the construction of a tetracycle related to pillaromycinone.

Scheme 2[10]



The critical annulation steps in these syntheses are displayed below (Schemes 2 and 3).

Scheme 3[11]

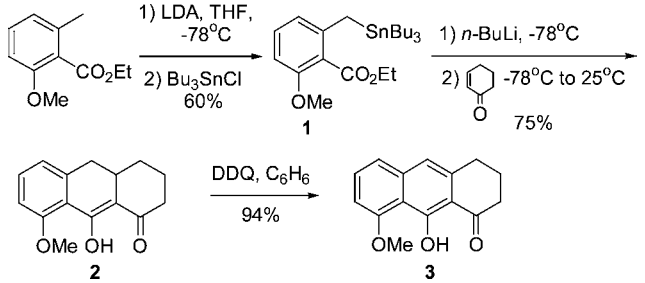


These syntheses clearly demonstrated the efficacy of the β-methoxylation strategy and the annulation came to be known as the Staunton−Weinreb protocol. Despite their obvious merit for regiocontrolled synthesis of *peri*-substituted naphthalene structural units, the two examples share a significant drawback in the context of natural product synthesis. These complex β-methoxycyclohexenones are synthesized from 1,3-dione precursors (or equivalents thereof), and in nonsymmetrical diones, this results in the formation of regioisomers[11] (2.5:1) or diastereomers[10] (1:1), which must be separated. Unless conversion of the undesired isomer into the desired one is a practical proposition, a substantial proportion of the enone is lost. Whereas suitable toluates are generally available the enones are much more valuable and represent most of the synthetic effort.

This difficulty could be overcome if cyclohexenones unsubstituted at the β-position could be employed without incurring the penalty of extensive polymerization. Our initial, not particularly successful attempt[12] to achieve this relied on separating the individual steps by in situ silylation of the enolate product of Michael addition. Although a moderate yield was achieved in this first step, the completion of the annulation required three more, and the overall yield was a disappointing 18%.

In continuing our efforts to solve this problem in pillaromycinone synthesis we explored many alternatives and finally settled on using tin−lithium exchange to generate the toluate anion rather than deprotonation (LDA/THF) because this would circumvent the production of diisopropylamine and thereby minimize enone polymerization. It had been noted earlier[2,13b] that cleaner deuteration of ethyl orsellinate and more efficient 1,2-addition to aldehydes resulted if the anion was generated in this manner. Treatment of the toluate anion produced in the usual way (LDA/THF, −78 °C) with tri-*n*-butyl chlorostannane gave the expected stannane **1**, which was isolated and purified by column chromatography (60%). We were unable to detect any distannylation product. The moderate yield was of little consequence because the toluate precursor is commercially available and easily synthesized[13] in large quantities. This stannane was transmetalated with *n*-butyllithium at −78 °C and treated with 2-cyclohexenone, and the reaction mixture was allowed to reach room temperature (Scheme 4).

Scheme 4



(9) Franck, R. W.; Bhat, V.; Subramaniam, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455.
(10) Dodd, J. H.; Starrett, J. E.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811.
(11) White, J. D.; Nolen, E. G.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1152.
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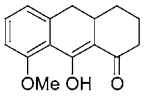
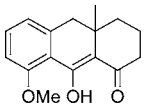
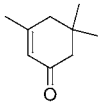
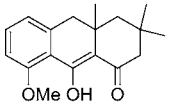
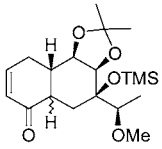
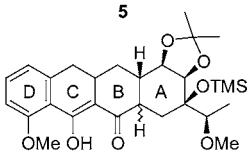
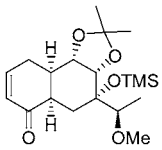
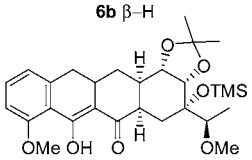
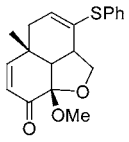
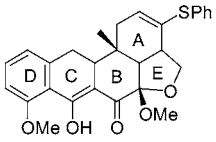
We were delighted to obtain a 75% yield of condensation product **2**, which was dehydrogenated by DDQ in benzene to anthracenone **3** (94%) previously characterized[14] as one of the products from the hydrogenation of 1-hydroxy-8-methoxy anthraquinone. The reaction was also attempted with six other substrates and in every case the condensation proceeded in very satisfactory yields (Table 1).

Table 1. Michael Acceptors and Annulation Products from the Stannane Modified Staunton−Weinreb Protocol

Entry	Michael Acceptor	Product	Yield
1		 **2**	75%
2		 **4**	74%
3		 **5**	83%
4a 4b		 **6a** α–H **6b** β–H	α = 71% β = 62%
5		 **7**	51%
6		 **8**	47%

The enones in entries 4a, 4b, and 5 are homochiral samples and were synthesized in our continuing program of research toward (+)- and (−)-pillaromycinones.[15] The tetracycles **6a** and **6b** have the appropriate absolute configuration for progression to (+)-pillaromycinone, the natural enantiomer. These compounds can be aromatized in ring C with DDQ as before.[12] In fact the AB trans tetracycle **6a** has already been dehydrogenated (ring C) in quantitative yield and is being carried forward to (+)-pillaromycinone. Product **8** is an interesting "hybrid" pentacycle with rings ABE of the halenaquinone precursor[16] and rings CD of pillaromycinone. Compounds such as halenaquinone containing a highly electron deficient furan ring (E) are of much interest as inhibitors of PI-3-kinase.[17] From these results it is clear that the simple modification described above remedies a significant practical problem associated with the Staunton−Weinreb annulation. It permits the employment of cyclohexenones, lacking a β-alkoxy substituent, as Michael acceptors and thereby transforms the process into one that offers new opportunities for the synthesis of complex polycyclic systems in an expeditious manner. We are continuing to test its limits with other cyclic enones and stereochemically complex substrates for natural product synthesis.

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Supporting Information Available: Experimental procedures and characterization data for **1**−**2** and **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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